DIAGNOSTIC CONCORDANCE AND CLINICAL OUTCOMES IN PATIENTS UNDERGOING FRACTIONAL FLOW RESERVE AND STRESS ECHOCARDIOGRAPHY FOR THE ASSESSMENT OF CORONARY STENOSIS OF INTERMEDIATE SEVERITY

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4718

ABSTRACT

Background

The ischemic consequences of a coronary artery stenosis can be assessed by invasive fractional flow reserve (FFR) or by non-invasive imaging. We sought to determine (i) the concordance between wall thickening assessment during clinically indicated stress echocardiography (SE) and FFR measurements and (ii) the factors associated with hard events in these patients.

Methods

223 consecutive patients who underwent SE and invasive FFR measurements in close succession were analyzed retrospectively for diagnostic concordance and clinical outcomes.

Results

At the vessel level, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of SE for identifying significant disease as assessed by FFR was 68%, 75%, 43% and 89% respectively. The greatest discordance was seen in patients with wall thickening abnormalities (WTA) and negative FFR. During a follow up of 3.6 ± 2.2 years there were 23 cardiovascular (CV) events (death and non-fatal myocardial infarction). The number of wall segments with inducible WTAs emerged as the strongest factor associated with CV events (HR 1.18 (1.05 – 1.34), p = 0.008). FFR was not associated with outcome. There was a significant increase in

event rate in patients with WTA/ negative FFR versus no WTA/ negative FFR (p=0.01), but no significant difference versus WTA/positive FFR (p=0.85)

Conclusion

In a patient population with significant CV risk factors, a normal SE had a high negative predictive value for excluding abnormal FFR. WTAs were associated with outcomes regardless of FFR value, suggesting that this is a superior marker of ischemia to FFR.

Keywords

Stress Echocardiography; Fractional Flow Reserve; Coronary Flow Reserve

INTRODUCTION

The ischemic consequences of a coronary artery stenosis can be assessed by invasive fractional flow reserve (FFR) or by non-invasive imaging. FFR determines the hyperemic pressure difference across a coronary artery stenosis, thus providing an index of the physiological significance of a coronary stenosis. FFR-guided revascularization improves event free survival, which includes subsequent revascularization, and FFR has emerged as a routine diagnostic test in clinical practice (1). Wall thickening abnormalities on stress echocardiography (SE) are well established for the detection and risk stratification of coronary artery disease (CAD) (2). Small studies have shown good agreement for the two techniques for the identification of ischemia-causing coronary stenosis, with FFR regarded as the gold standard (3,4). However, the gold standard FFR cutoffs themselves were originally based on agreement with noninvasive imaging, thereby revealing logical inconsistency.

CFR (coronary flow reserve) represents the ability of the coronary arteriolar bed to vasodilate and hence increase myocardial blood flow in response to increasing cardiac metabolic demands, and is blunted by the presence of flow limiting coronary stenoses, diffuse non-obstructive coronary disease and microvascular disease. Since CFR represents the increase in hyperemic flow compared with baseline flow, in conditions where resting flow in increased e.g. with inflammation, hyperemic flow might be quite normal while CFR would be judged to be "reduced". Reduced CFR may occur by any combination of the above mechanisms, and lead to the inability to increase

myocardial blood flow adequately to meet the oxygen demand during stress, thus precipitating ischemia (5). The subendocardial layer bears the impact of this mismatch due to the high endocardial pressure in this part of the myocardium. Since the subendocardial layer is normally responsible for wall thickening, this is dramatically reduced which is detected during SE. Thus wall thickening is a surrogate marker of coronary flow reserve. CFR determined quantitatively has been shown to predict hard cardiac events (6,7) and SE, an indirect measure of CFR, similarly predicts hard cardiac events (2).

On the other hand FFR does not look at flow reserve, but measures the difference in pressure across an epicardial coronary arterial stenosis. The degree of pressure drop across the stenosis is dependent upon the magnitude of flow, which is governed by CFR. If flow is reduced, due to microvascular disease for example, the pressure drop may be mitigated and FFR may be normal in the presence of a severe stenosis. It is therefore unsurprising, that invasive FFR and CFR results are discordant in 30% to 40% of coronary stenoses (10). Both FFR and CFR have been shown to predict outcome but unlike CFR, the outcome with FFR is mainly driven by repeat revascularization (11, 12).

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The purpose of this study was to determine (i) the concordance between wall thickening assessment and FFR during clinically indicated SE and FFR measurements and (ii) the factors associated with hard events in patients assessed in our daily routine clinical practice. We hypothesized that since wall thickening is a marker of coronary flow reserve, this is a better indicator of ischemia than FFR and thus has a stronger association with CV events.

METHODS

Consecutive patients undergoing clinically indicated SE and angiography with invasive FFR measurements within 6 months for the evaluation of known or suspected CAD between January 2008 and June 2016 were analysed retrospectively. Exclusion criteria included patients with acute coronary syndrome or revascularization procedures between the 2 studies, or deterioration in clinical symptoms. The study was approved by the institutional review board. Clinical characteristics and follow-up data were collated by reviewing hospital records, contacting patients or a family member, and contacting general practitioners. A national mortality database was used to identify deceased patients. The date of the last review or consultation was used to calculate the duration of follow-up up to 1st January 2017.

Stress Echocardiography

All SE studies were performed using either treadmill exercise or pharmacological (dobutamine-atropine) stress as described previously (13). As per protocol heart rate lowering medications were withheld for 48hrs prior to testing. In summary, exercise stress was the preferred modality, and in patients unsuitable for exercise, dobutamine was infused in 3 minute dose increments, starting from 10mcg/kg/min and increasing to 20, 30 and 40mcg/kg/min if there were no resting wall motion abnormalities, otherwise a viability protocol was used commencing at 5mcg/kg/min. Parasternal long axis, short axis and apical 4-chamber, 2-chamber and 3-chamber images were obtained at rest and peak stress (iE33 Philips Medical Systems, Eindhoven, the Netherlands). In patients in whom the endocardial borders of ≥2 contiguous segments were not visualised, the ultrasound contrast agent Sonovue (Bracco, Milan, Italy) was

given by intravenous bolus injection (0.3 mL) and flushed with saline. The final SE result was based on the interpretation of the expert cardiologist (RS)

The SEs were reported as normal (normal wall thickening at rest and stress) or ischaemic (inducible wall thickening abnormality ≥1 segment at peak stress or presence of biphasic response in patients with resting wall thickening abnormalities during low and high doses of dobutamine).

Coronary Angiography and FFR

Coronary angiography was performed where clinically indicated and in most cases where stress echocardiography was positive for inducible ischemia. In patients with persistent symptoms and normal SE, angiography with FFR measurements may have been performed.

Coronary angiography was performed as per standard practice via either the femoral or radial approach. Coronary stenosis severity was based on visual assessment. The pressure wire (Pressure Wire Aeris, St Jude Medical Inc., MN, USA) was calibrated and electronically equalized with the aortic pressure before being placed in the desired position distal to the lesion in coronary artery being interrogated. Intracoronary nitroglycerin was used as per protocol before the adenosine infusion to negate the effects of any vasospasm. Intravenous adenosine was administered at a dose between 140-180mcg/kg/min through a large bore intravenous line in the antecubital fossa. The resting distal coronary pressure to aortic pressure ratio (Pd/Pa) was continuously recorded throughout using the St Jude Medical QUANTIEN system, as calculated by dividing the mean coronary pressure measured with the pressure sensor placed distal to the stenosis by the mean aortic pressure measured

through the guide catheter. At a steady state of maximal hyperemia, the nadir FFR was recorded.

FFR measurements were performed on all major epicardial arteries deemed to have intermediate stenosis (30-80%), where the presence or absence of a severe stenosis was not evident visually. It must be noted that if SE demonstrated ischaemia in a coronary territory, and quantitiative angiography demonstrated < 30% stenosis, FFR would not have been clinically indicated. Conversely, on the few occasions where SE did not demonstrate ischaemia in a territory, and an intermediate stenosis (30-80%) was seen on quantitative angiography, FFR would have been performed. An FFR value of ≤0.8 was chosen as the cut off for abnormal based on previous multicenter studies (1). Caffeine and all food products were withheld in patients for 12 hours before FFR measurements.

Revascularization

Revascularisation was performed in vessels where FFR ≤ 0.80 (irrespective of SE results) where possible and in bystander vessels deemed to have significant stenosis and therefore viewed as needing revascularization. Where FFR was > 0.80, revascularisation was not performed irrespective of SE results.

Endpoint definition

The principal end-points of interest for this analysis were cardiovascular (CV) death (due to myocardial infarction (MI), cardiac arrhythmias or heart failure) and non-fatal MI (NFMI), with patients censored at the time of event or at the last follow-up. NFMI was defined by the standard criteria of ischaemic chest pain associated with an

elevation of cardiac enzymes with or without electrocardiographic changes. For patients with multiple events, only the first event was considered.

STATISTICS

Categorical variables are expressed as percentages and continuous variables as mean ± SD. Spearman rank correlation coefficients were used to compare SE and FFR data. Cox regression analysis was performed to assess the prognostic impact of clinical variables, SE parameters and FFR on the time to a hard event. FFR was entered into the regression analysis as both a binary and continuous variable. Patients without a hard event were censored at the time of last follow-up. Kaplan-Meier survival curves were constructed showing the time to a hard event and were compared by the log-rank score test. For all tests, a value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 23.0 (IBM Corp, Armonk, NY).

RESULTS

223 patients met the eligibility criteria. Table I illustrates the patient demography of the 223 patients who underwent combined SE and invasive FFR measurements. The mean age was 66.4 ± 11.5 years and 154 (69%) patients were male with the majority having significant CV risk factors (almost 50% had diabetes mellitus (DM), over 80% had systemic hypertension and almost 70% had hypercholesterolemia) The mean left ventricular ejection fraction (LVEF) was 55% ± 7% with 27 (12%) patients demonstrating LV dysfunction (LVEF<50%). Resting wall thickening abnormalities were present in 36 (16%) patients and inducible ischemia was present in 136 (61%) patients. In most cases (83%), SE preceded angiography. Of 223 SEs, 125 (56%)

patients underwent Dobutamine SE with the remainder undergoing Exercise SE. Most patients (86%) received contrast agent. Chest pain was by the far the most common indication for testing (79%).

Table 1 : DEMOGRAPHICS OF STUDY POPULATION

PATIENT CHARACTERISTIC	N (%)
NUMBER OF PATIENTS	223
AGE	66.4
MALE GENDER	154 (69)
INDICATION	
CHEST PAIN	176 (79)
BREATHLESSNESS	20 (9)
SYNCOPE	4 (2)
POST-MI	23 (10)
SMOKER	80 (36)
HYPERTENSION	189 (85)
DIABETES MELLITUS	96 (43)
HYPERCHOLESTEROLAEMIA	158 (71)
FAMILY HISTORY	65 (29)
PVD	25 (11)
AF	16 (7)
CKD	26 (12)
PREVIOUS CAD	106 (47)
MYOCARDIAL INFARCTION	37 (17)
PCI	55 (25)
CABG	14 (7)
LVEF < 50%	27 (12%)
RESTING WALL THICKENING ABNORMALITIES	36 (16)
INDUCIBLE WALL THICKENING ABNORMALITIES	136 (60)
WALL MOTION	
MEAN $WMSI_{REST}$	1.09 (0.27)
MEAN $WMSI_{STRESS}$	1.21 (0.26)
CARDIAC MEDICATIONS	
ANTIPLATELET AGENTS	185 (83)
BETA-BLOCKER	135 (61)
CCB	65 (29)
STATIN	196 (88)
ACEi/ARB	171 (77)
NITRATES	67 (30)
SE	
CONTRAST	192 (86)
DOBUTAMINE	123 (55)

FFR readings

FFR values ranged from 0.54-1 (mean 0.84 ± 0.006). FFR was significantly lower in patients with a positive SE than in patients with a negative SE result (0.82 ± 0.08 versus 0.87 ± 0.06, $p<0.001$), although a large overlap of the individual data was observed between the two groups (Fig 1). The correlation between the number of segments with wall thickening abnormalities (WTA) and FFR was weak but statistically significant ($r=0.36$, $p<0.001$).

Diagnostic accuracy of SE

A total of 259 vessels in 223 patients were evaluated. The average stenosis severity was 53% ± 12% (range 30-80%). From 259 vessels analysed, the Left Anterior Descending Artery, Right Coronary Artery, Left Circumflex Artery and Left Main Coronary artery were involved in 145 (56%), 54 (21%), 37 (14%), 21 (8%) respectively, with 2 vessels being grafts.

FFR measurements were positive in 56 (22%) and negative in 203 vessels (78%), using a cut off of ≤ 0.80. At the vessel level, of the 259 vessels, SE was positive in 87 (34%). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of SE for identifying significant disease as assessed by FFR was 68%, 75%, 43% and 89% respectively. In 79 patients, there was single vessel disease on angiography. Here, the sensitivity, specificity, PPV and NPV were 81%, 63%, 36% and 93% (Table 2). Similar to the overall results the negative predictive values of SE were high i.e. 85%, 97%, 100% and 85% for left anterior descending artery, right coronary artery, left circumflex artery and left main stem respectively

with lower respective positive predictive values i.e. 46%, 18%, 57% and 71% (Table 3).

At the patient level, FFR was positive in 54 (24%) patients and inducible WTA occurred in 136 (61%) patients. The overall sensitivity, specificity, PPV and NPV were 91%, 51%, 36% and 94% respectively in patients where FFR was measured when an intermediate stenosis (30%-80%) was seen (Table 2). There were no significant changes in diagnostic accuracy with and without contrast or with mode of stress (sensitivity, specificity, PPV, NPV were 72%, 77%, 43% and 92% for exercise and 65%, 74%, 43% and 87% for dobutamine respectively). Figure 2 (with video supplement) gives an example of a patient with discordant positive SE and negative FFR.

Table 2 : Concordance between SE and FFR per vessel, per vessel in patients with single vessel disease and per patient

Per vessel	SE +	SE -
FFR +	38	18
FFR -	50	153
Per vessel (single)		
FFR +	13	3
FFR -	23	40
Per patient		
FFR +	49	5
FFR -	87	82

Table 3 : Concordance between SE and FFR according to vessel location

	Sensitivity	Specificity	PPV	NPV
LAD	63	75	46	85
RCA	75	70	18	97
LCx	100	87	57	100
LMS	71	86	71	85

Follow up

Of the 223 patients analysed, 9 patients were lost to follow up. The remaining 214 patients (95%) were followed up for a mean interval of 3.6 ± 2.2 years. Revascularization was performed in 97 (43%) patients, of which 9 patients underwent surgical revascularization. In total, there were 23 cardiovascular (CV) events – 17 NFMI and 6 CV deaths. Univariable cox regression analysis showed that $WMSI_{rest}$ (HR 3.26 (1.04-10.2), p = 0.04) and number of segments with inducible WTA (HR 1.20 (1.07-1.36), p = 0.003) were associated with outcome. FFR was not associated with outcome when entered as a binary or continuous variable. Revascularization was also not associated with outcome. When the 19 patients with troponin positive acute coronary syndrome were removed, number of segments with inducible WTA remained associated with CV events (p = 0.01). Since the number of events were modest, multivariate analysis was not performed.

Log rank test analysis showed that a cut-off of >2 segments with inducible WTA was best associated with CV events compared to 2 or less segments (p=0.004). This is shown in Fig 3 using Kaplan-Meier survival curves demonstrating the freedom from CV events for the duration of follow up. CV event rate was 1.6%/year in patients with no significant ischemia versus 4.3%/year in those with significant ischemia. Figures 4 and 5 demonstrate the Kaplan-Meier curves for freedom from CV events for patients who were (i) SE positive-FFR negative and SE negative-FFR negative and (ii) SE positive-FFR negative and SE positive-FFR positive. There was a significant (p=0.01) increase in event rate in SE positive-FFR negative patients over SE negative-FFR negative patients (annual event rate 4.4% versus 1.4%). The event rates in the SE

positive–FFR positive and SE positive-FFR negative groups were similar (4.3% versus 4.4%, p=0.85).

DISCUSSION

To the best of our knowledge, this is the largest series of patients to have undergone both SE, a marker of CFR, and invasive FFR measurement in close succession and the first study to report on hard event rates. The patient population was elderly with significant cardiovascular risk factors - a population commonly seen in our daily routine clinical practice. We have shown that in this population on a per patient basis, when FFR was abnormal (FFR<0.80), almost all patients (91%) demonstrated ischemia during SE. On the contrary, when FFR was in the normal range ischemia during SE was provoked in almost half of such patients (so called 'false positive' SE). However, these patients with a 'false positive' SE (normal FFR) had an event rate not significantly different from patients with a 'true positive' SE (abnormal FFR), and significantly higher than in patients with a 'true negative' SE. Indeed in this population, it was SE parameters and not FFR that were associated with hard cardiovascular events. FFR is therefore a poor indicator of ischemia.

Diagnostic performance of SE versus FFR

Several studies have reported similar diagnostic accuracy for SE when compared with FFR, as we have demonstrated (3, 4). The vessel sensitivity of SE was noticeably higher for single versus multi-vessel disease, since in multi-vessel disease SE precipitates ischemia in the myocardium subtended by the most severe coronary stenosis, at which point the patient is symptomatic on exercise or the pharmacological test is terminated. A significant inverse linear correlation was present between number

of ischemic segments during SE and FFR. However, the correlation is modest since FFR assesses the role focal epicardial stenosis resistance contributes to the overall resistance in the entire coronary circuit of that territory, but other factors contribute to ischemia. There was a discordance rate of 40%, with the greatest source of discrepancy in vessels with a normal FFR - an observation also made in a recent study (14)

Pathophysiologic basis of FFR and SE determined ischemia

There are several causes of myocardial ischemia in a patient with ischemic heart disease, of which epicardial focal obstructive CAD is common. However co-existing diffuse non-obstructive CAD and microcirculatory disease may contribute significantly to myocardial ischemia and may even cause ischemia in isolation (5). Whether any of the above-mentioned conditions causes ischemia depends on the ability of the myocardium to maintain sufficient blood flow in the presence of increased myocardial oxygen demand which is represented by the CFR. The extent and severity of the reduction of wall-thickening detected by SE, is linearly related to the reduction in CFR after a threshold level (15). CFR has been shown to be a powerful predictor of hard cardiac events in patients with CAD (6,7). Similarly, SE has been shown to predict such outcomes (2).

FFR has been shown to predict outcome, but data on the prediction of hard cardiac events is inconsistent (1,12,16). Unlike CFR which measures **flow**, FFR measures **pressure**. FFR assesses pressure in the non-stenosed coronary artery segment proximal to the stenosis, and beyond the stenosed segment at rest and during hyperemia. The pressure drop across a coronary stenosis is dependent on the

transtenotic flow rate, which during FFR measurement is driven by CFR. Therefore although on average high FFR values represent non-significant lesions, low flow during hyperemia caused by a diseased microcirculation and non-obstructive CAD can lead to a misleadingly high or normal FFR result (5). On the other hand SE will precipitate myocardial ischemia because myocardial oxygen demand will exceed the hyperemic flow, which is obtunded due to low CFR. This explains the not so infrequent occurrence of a positive SE and a normal FFR in the study cohort, which is elderly increasing the likelihood of extensive CAD, albeit non-obstructive, that compromises CFR.

The fact that a positive SE irrespective of FFR is a marker of myocardial ischemia, is supported by high CV event rate in this group (4.3%/year) compared to only 1.6% in patients with a normal SE, in a population where the prevalent CV event rate is high (2.9%/year). Our study also showed in concordance with the concept postulated, that FFR in the normal range does not portend a benign outcome (CV event rate 2.6%/year). This has also been shown by other authors (12,16). Thus FFR, as employed in the cardiac catheterisation laboratory, is not a very good standard to use for determining whether end-organ hypoperfusion is or is not present.

Similarly echocardiography-derived doppler coronary flow reserve, which compares peak diastolic Doppler coronary flow velocity at baseline with peak diastolic Doppler flow velocity with hyperemia, is a velocity-dependent parameter and is an imperfect surrogate of myocardial perfusion.

Another mechanism that explains the discrepant results between FFR and SE is that while at rest the greatest resistance to myocardial blood flow is offered by the vessel stenosis, during hyperemia capillary resistance is the predominant source of resistance

to myocardial blood flow (17). This occurs through decreased capillary recruitment to maintain transcapillary hydrostatic pressure. With reduced capillary blood flow, ischemia is precipitated when myocardial oxygen demand outstrips the supply, resulting in reduced wall thickening detected by SE. However, coronary blood flow does not increase significantly because of increased downstream resistance. In patients with more severe stenosis the resistance becomes uniform in the coronary tree (18)

Comparison with other studies

This is the largest patient cohort undergoing both FFR and SE and exceeds the combined number from several meta-analyses (8, 9). A prospective study of FFR-SE in patients with single vessel disease showed, similar to the present retrospective study, a sensitivity and specificity of 83% and 73% respectively where contrast and dobutamine stress were used in all cases (4). A recent study, using myocardial contrast echocardiography (MCE) which assesses myocardial perfusion and wall motion simultaneously, showed excellent sensitivity for MCE (93%) for predicting abnormal FFR, but numbers were smaller and patients predominantly had single vessel disease (where sensitivity was 81% in the present study) (14). The higher sensitivity of MCE can be explained by the fact that perfusion abnormalities precede wall thickening abnormalities (19,20). Similar to the present study a large proportion of negative FFR patients, had positive MCE (57%) but unlike the present study hard outcomes were not examined (14). In a retrospective analysis in patients undergoing combined invasive CFR measured by coronary flow velocity and FFR measurements, during long term follow up, the highest event rate occurred in lesions with discordant

normal FFR-abnormal CFR. Lesions with abnormal FFR-normal CFR had similar event rates to concordantly normal CFR and FFR (10).

Clinical implications

Randomized studies have shifted the evaluation of stenosis severity from angiography to physiology, specifically by using FFR. An FFR-guided strategy requires that only coronary arteries with FFR < 0.80 are treated meaning a significant number of intermediate lesions are not managed invasively. However, the pathophysiological basis of FFR measurements and the present data suggest that the result of FFR measurements should be carefully evaluated in the context of the patients' symptoms. In patients with multi-vessel disease complaining of anginal symptoms, FFR guided stent implantation may be better than SE for the relief of symptoms but not for predicting hard outcomes, as although SE may not identify all vessels causing myocardial ischemia it nevertheless is associated with outcome. Where FFR is negative in a patient with persistent symptoms and positive SE, further evaluation with advanced coronary imaging (e.g. IVUS, optical coherence tomography) or invasive CFR may be indicated. With the high event rate in this subset, such patients may benefit from revascularization and at the very least, escalated secondary prevention. Such limitations of FFR are well recognized by interventional cardiologists (21). The above findings have obvious implications, but need to be corroborated in large multicenter prospective studies, such as the ongoing ISCHEMIA study (22).

Study limitations

The findings from this study should be interpreted in the context of some limitations. The population studied is heterogenous including patients with stable angina and those with troponin positive acute coronary syndromes. However on excluding patients with troponin positive events, inducible WTAs not FFR, continued to be associated with outcomes. There is a selection bias in that not all patients would undergo SE and FFR, except where clinically indicated. It is likely that the majority of patients who had undergone FFR when SE was positive, had an intermediate stenosis on angiography and FFR was used to confirm the functional significance of the lesion despite a positive SE. It's possible that anatomically severe lesions would have been intervened on without functional measurements. Conversely, lesions deemed mild may have not undergone invasive pressure measurement. Although the event rate in these scenarios would not have been captured, we have reported on real world experience which has greater clinical relevance, and in practice there is not a blanket approach to FFR. The study was also retrospective, but this is a study testing a unique hypothesis and the study design allowed for long term follow up and inclusion of relatively large numbers. It is possible that with much larger numbers and more events, FFR may have become a predictor of CV outcomes.

Conclusion

This 'proof of concept' study is the first to examine hard events in patients undergoing both SE, a marker of CFR, and invasive FFR measurements We have shown SE parameters to be strongly associated with CV outcomes. Patients with discordant SE positive-FFR negative have much worse outcomes compared to patients with concordant negative SE-FFR. These findings have clinical implications.

Disclosures : Regarding conflicts of interest, RS has previously received honoraria from Bracco (Milan, Italy), Philips Healthcare (Eindhoven, Netherlands) and Lantheus Medical Imaging (North Billerica, MA). All other authors report no relevant conflicts of interest to declare.

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FIGURE LEGENDS

FIG 1: Box Wistar plot comparing FFR values according to the presence or absence of inducible ischemia on SE.

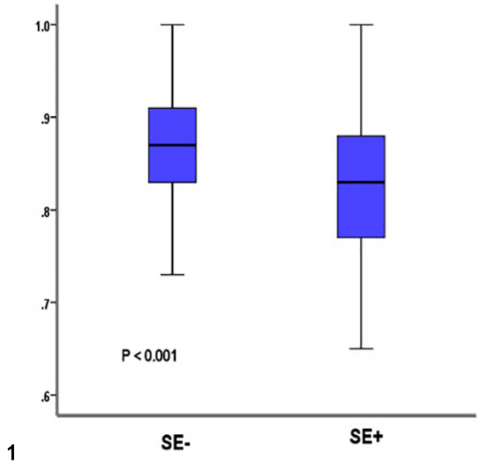


FIG 2: An example of a patient with inducible wall thickening abnormalities in the Left Anterior Descending Artery territory during exercise echocardiography. Subsequent coronary angiography demonstrated proximal LAD stenosis of 50% (white arrow) and a FFR across the lesion of 0.92.

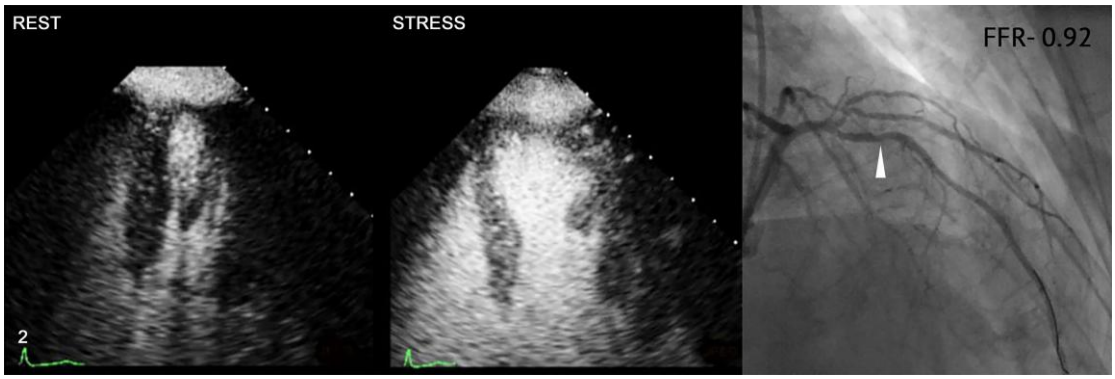
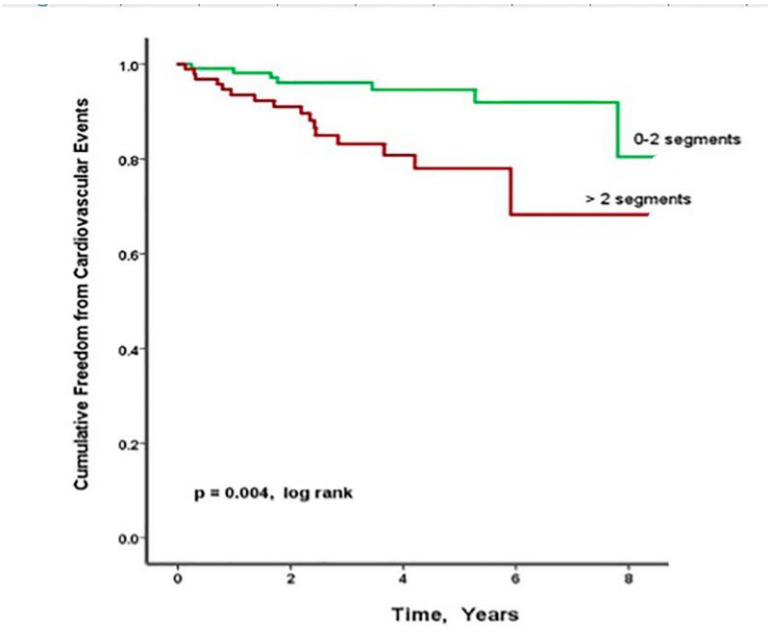


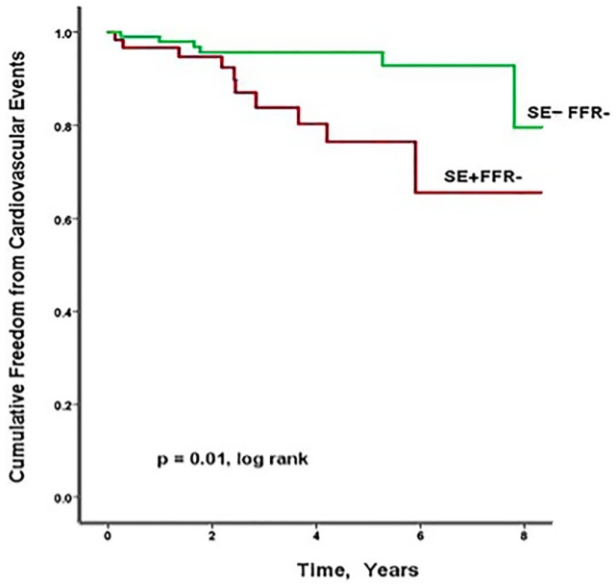
FIG 3: Kaplan–Meier survival curve demonstrating freedom from CV events based on stress echocardiography result (significant ischemia versus no significant ischemia).



NO. AT RISK					
0-2 segments	117	113	112	111	110
> 2 segments	97	91	83	81	81

3

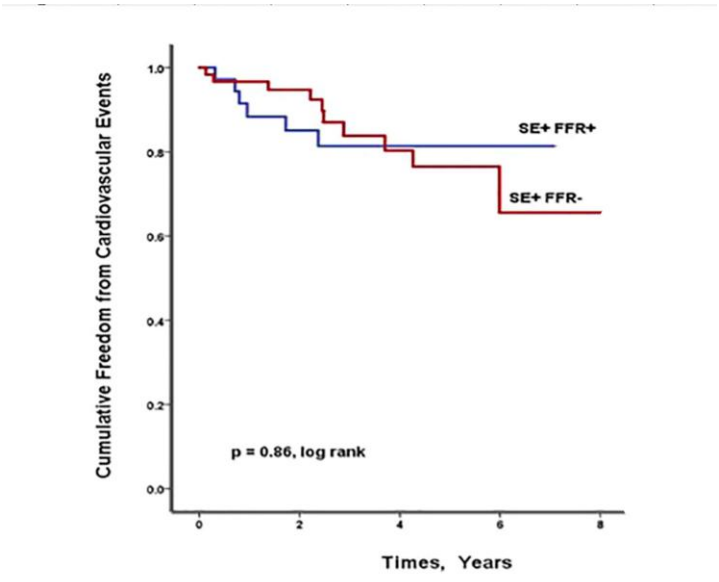
FIG 4 : Kaplan–meier survival curve demonstrating freedom from CV events in SE positive FFR negative versus SE negative FFR negative patients



NO. AT RISK					
SE- FFR-	105	101	101	100	99
SE+ FFR-	63	60	55	53	53

4

FIG 5 : Kaplan–meier survival curve demonstrating freedom from CV events in SE positive FFR positive versus SE positive FFR negative patients



NO. AT RISK					
SE+ FFR-	63	60	55	53	53
SE+ FFR+	36	31	30	30	30

5

Figure

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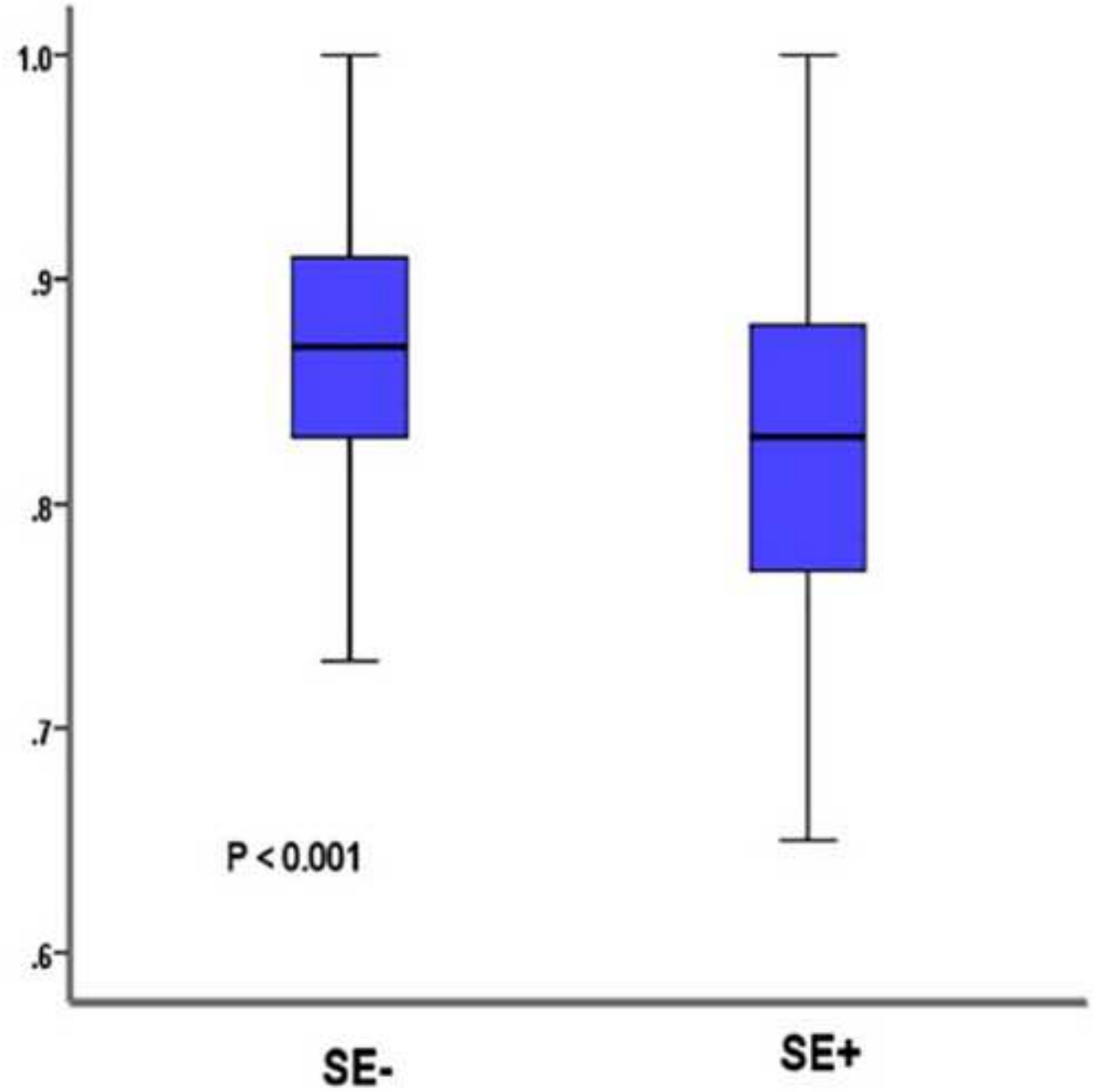

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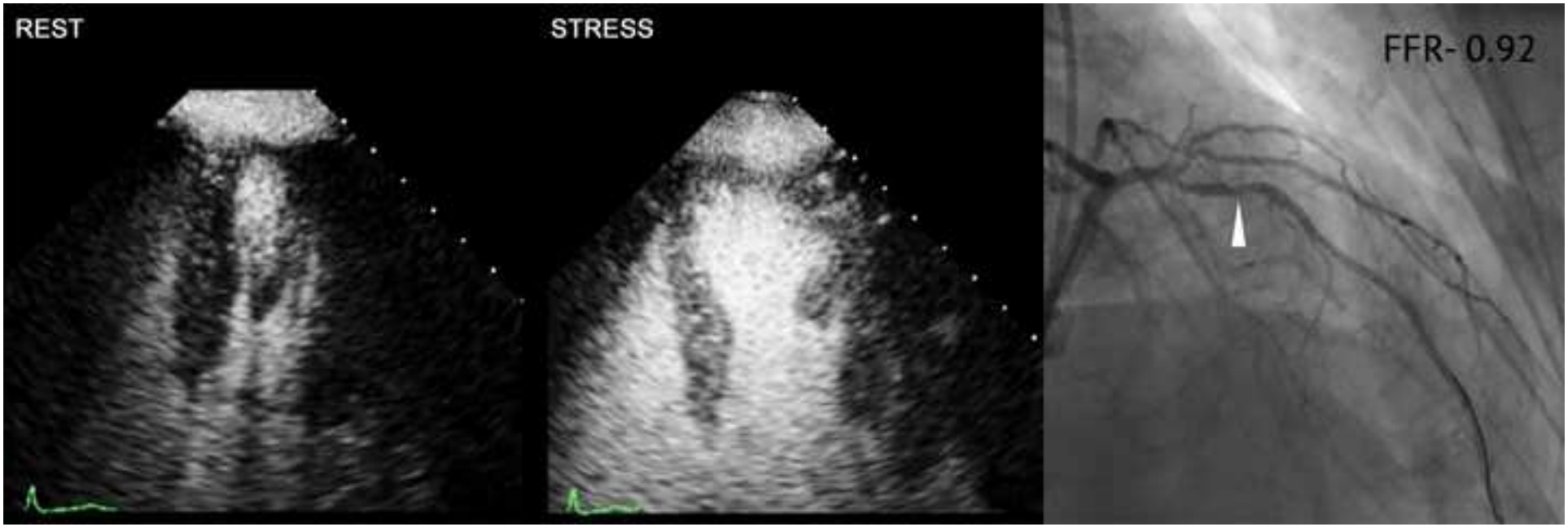

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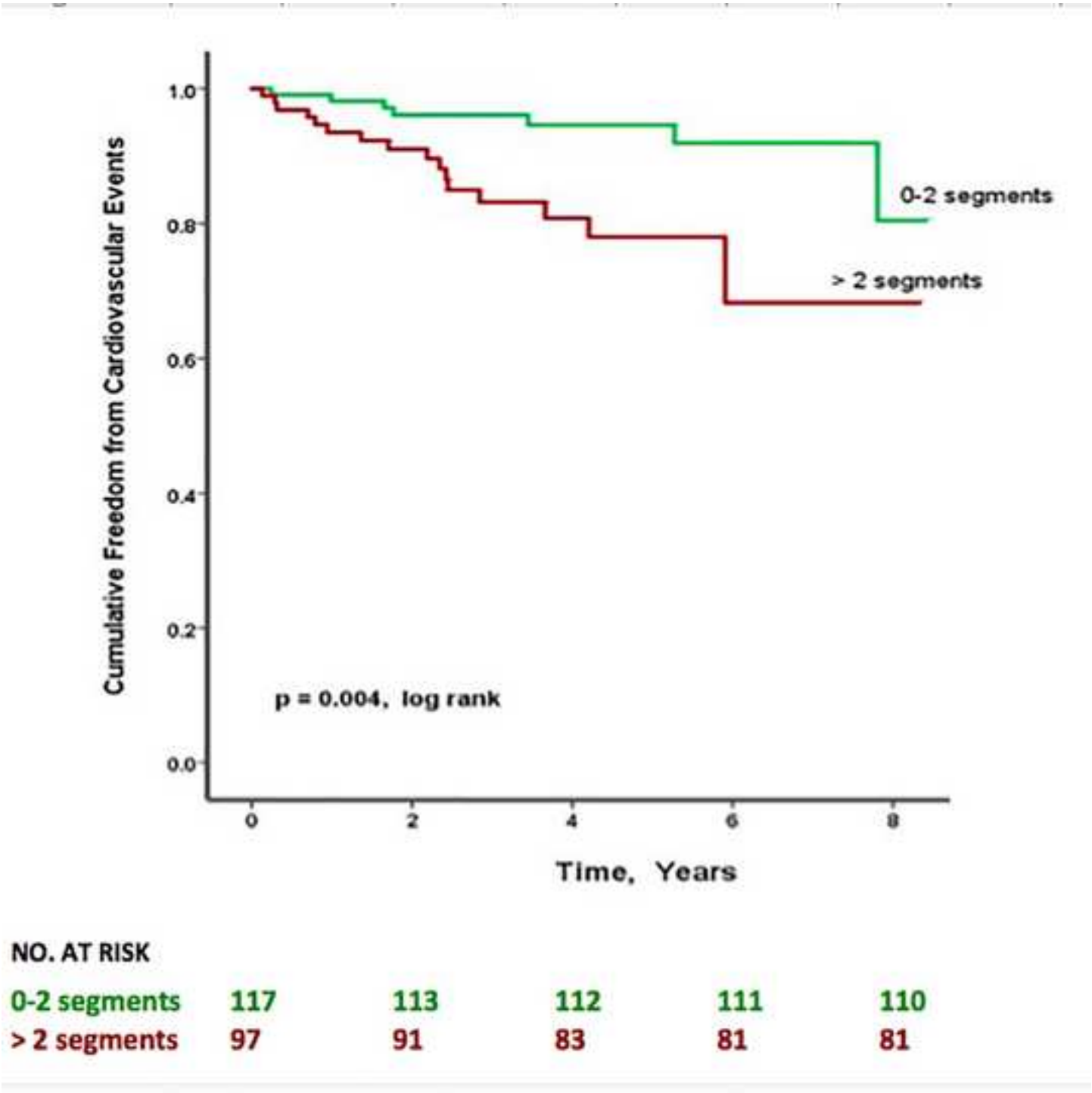

Figure

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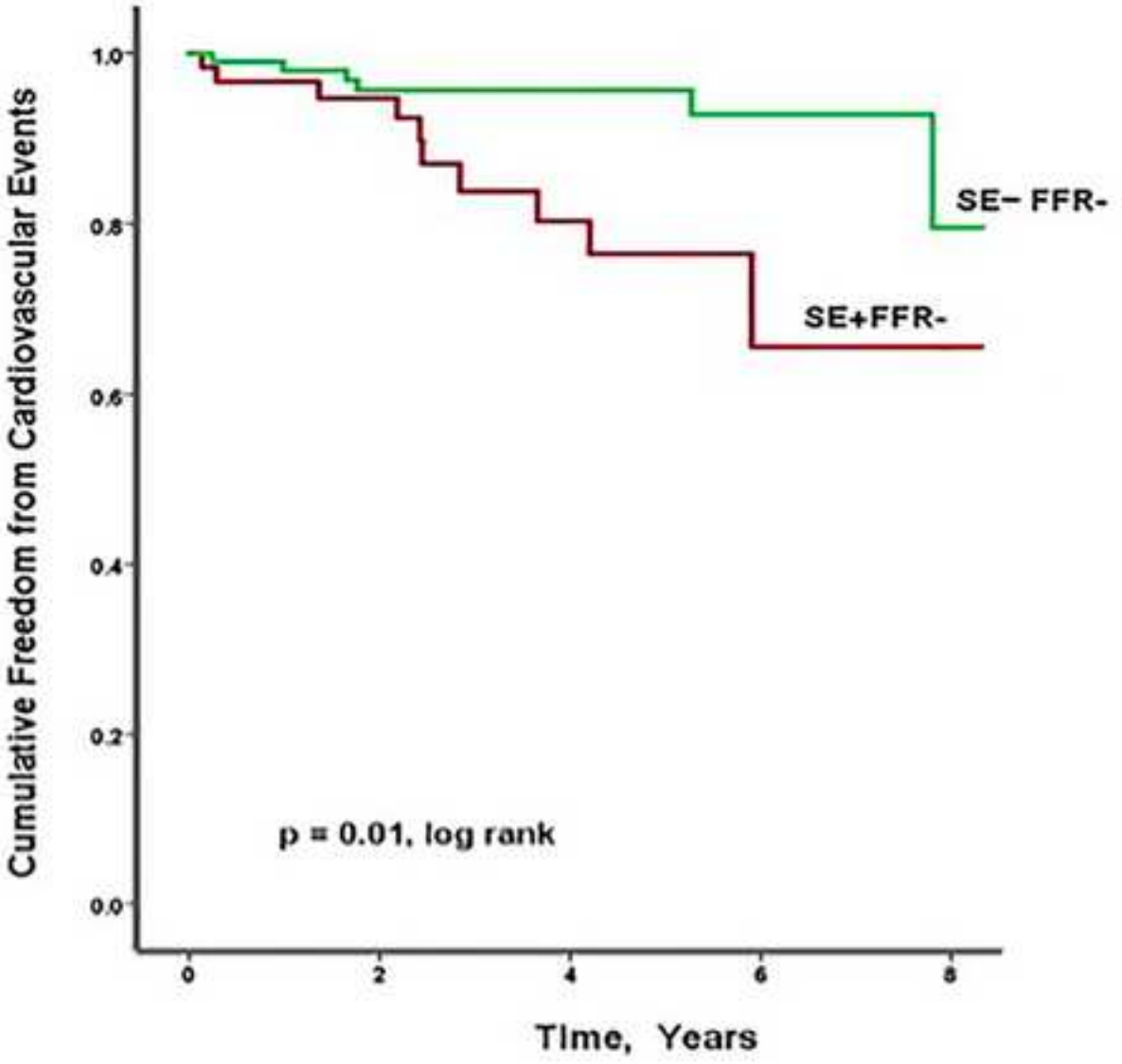

NO. AT RISK					
SE- FFR-	105	101	101	100	99
SE+ FFR-	63	60	55	53	53

Figure

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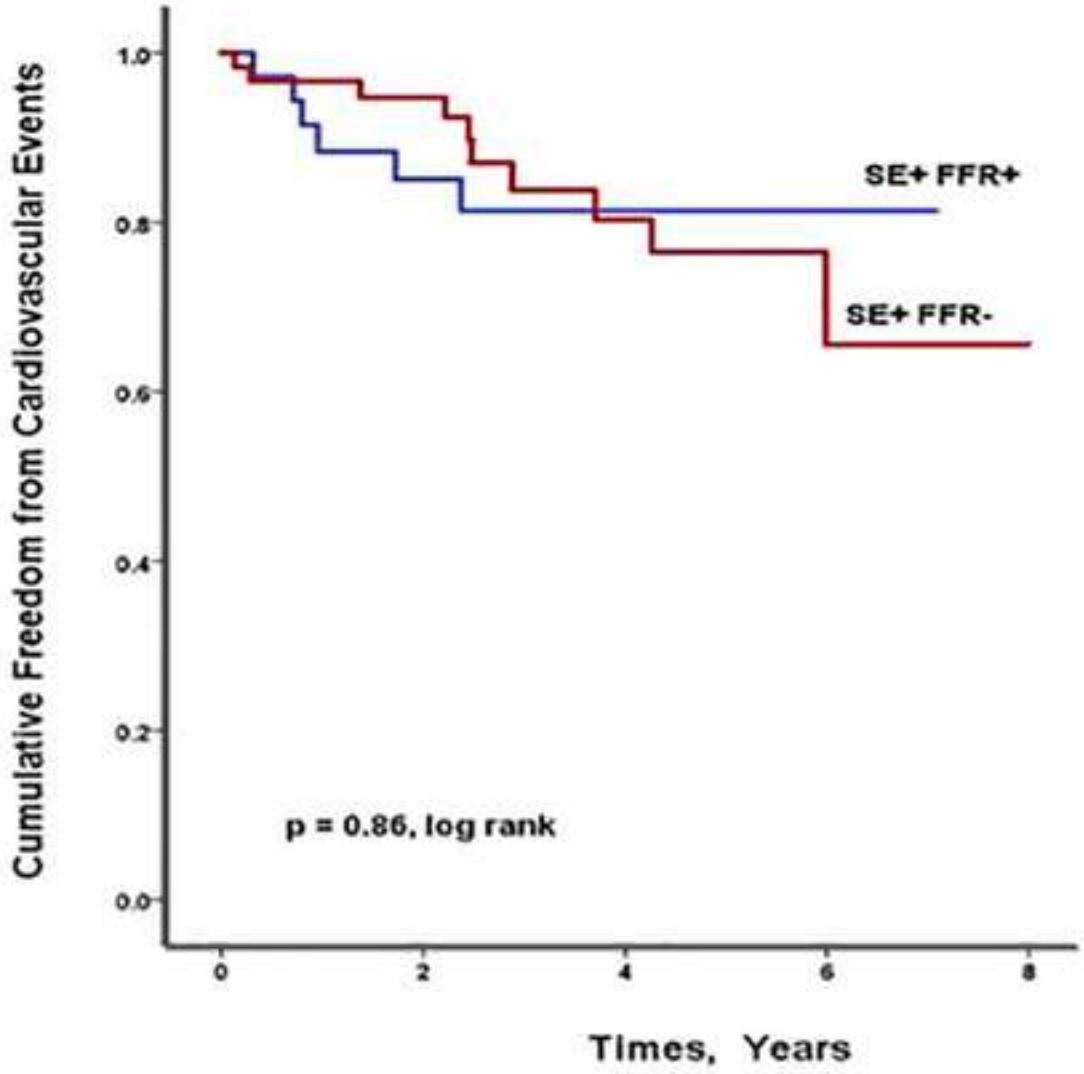

NO. AT RISK					
SE+ FFR-	63	60	55	53	53
SE+ FFR+	36	31	30	30	30

Video Still

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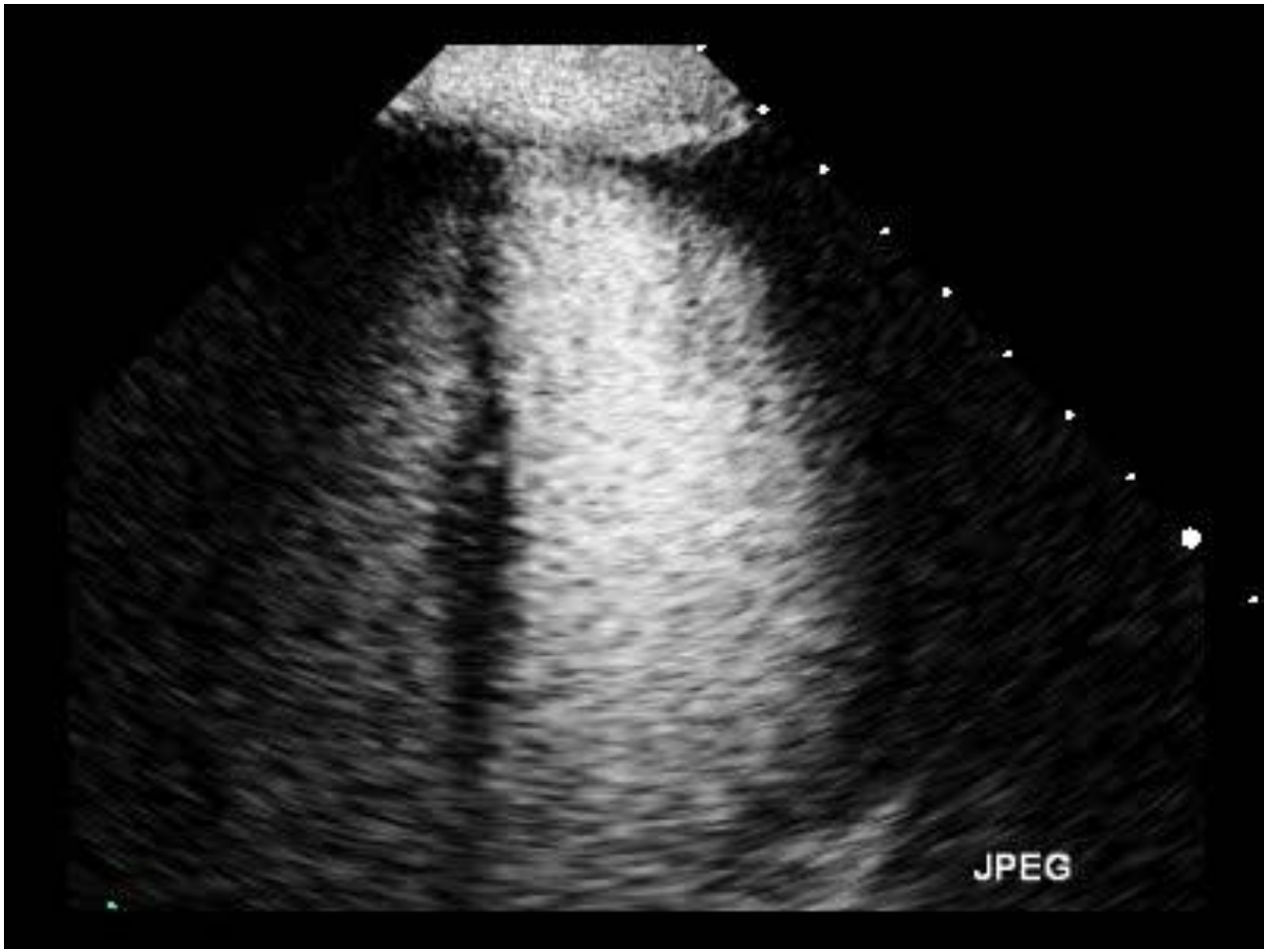

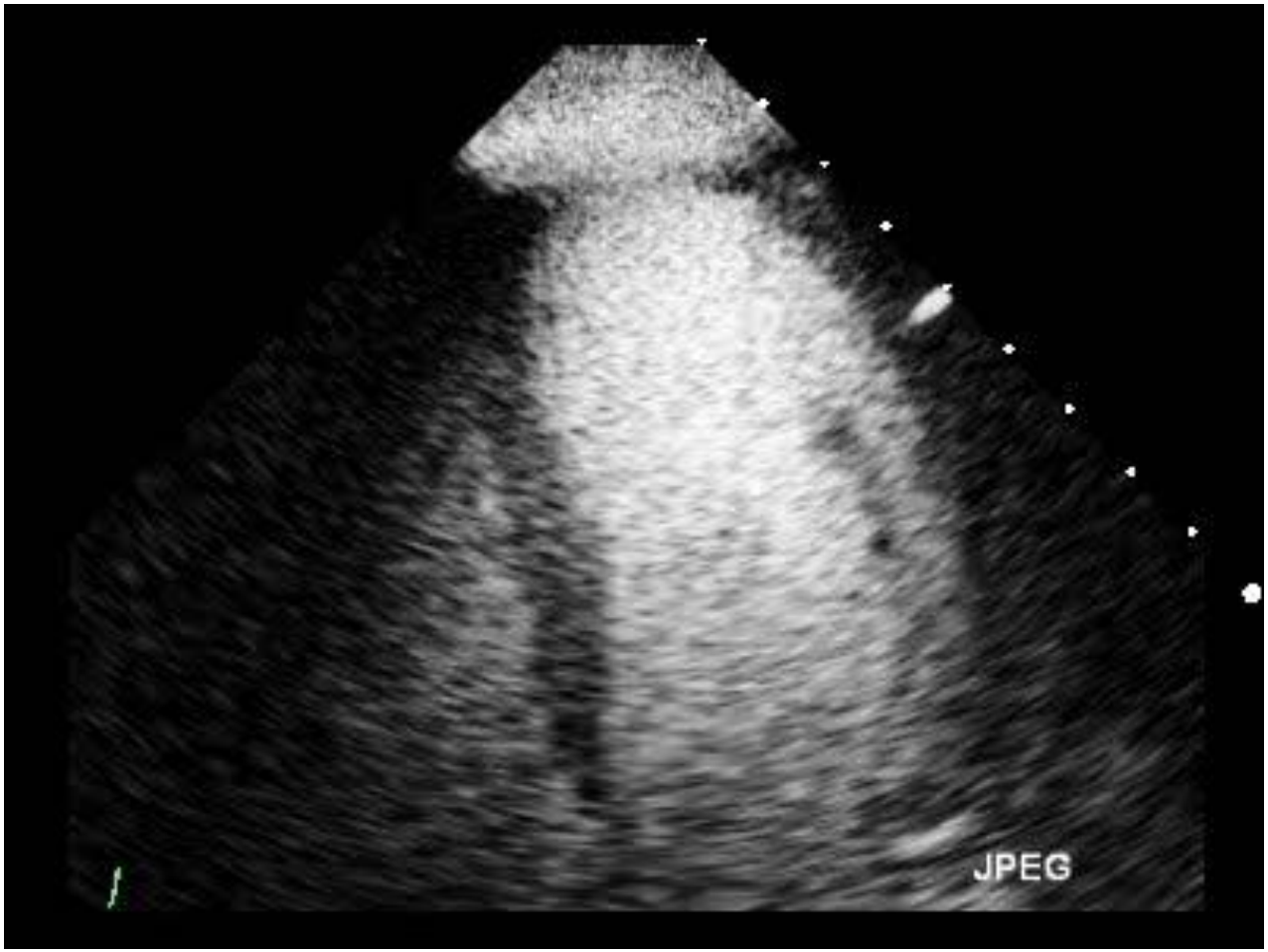
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