Predictive value of ventricular premature beats for subsequent ischaemic heart disease in apparently healthy subjects

P. Bjerregaard, K. E. Sorensen and H. Molgaard

University Department of Cardiology, Skejby Sygehus, 8200 Aarhus N, Denmark

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From 1978 to 1980, 260 healthy subjects, 40–79 years of age, underwent 24 h ambulatory electrocardiography in order to determine the prevalence and complexity of ventricular premature beats (VPBs) in adults without apparent heart disease. The number of types of VPBs seen in 5% or less were considered 'abnormal' and the present follow-up study undertaken in order to assess the significance of such 'abnormal' VPBs as predictors of subsequent ischaemic heart disease (IHD).

Information concerning cardiac events within the follow-up period was available in 237 subjects. Nine were lost to follow-up and 24 refused clinical examination. IHD was documented in 13 (eight myocardial infarction, five angina pectoris). 'Abnormal' VPBs occurred in six out of 13 (46%) who later developed IHD compared to only 24 out of 213 (11%) without IHD (P < 0.001). The presence of either more than 900 VPBs 24 h⁻¹ or ventricular tachycardia of more than three beats, identified five out of 13 patients with IHD (sensitivity 38%), whereas 210 out of 213 with no evidence of IHD at follow-up were identified (specificity 98%). Four out of seven who initially had more than 900 VPBs 24 h⁻¹ had IHD on follow-up.

Our results have demonstrated a strong positive association between 'abnormal' VPBs observed in a random 24-h electrocardiographic recording of apparently healthy subjects 40–79 years of age and subsequent IHD. They also suggest that a 24-h ECG may be useful for the assessment of coronary risk even in asymptomatic subjects.

Introduction

Of all disturbances in cardiac rhythm none has engendered as much interest as ventricular premature beats (VPBs). Studies using standard 12-lead ECGs for separating people with VPBs from those without, have generally failed to show any prognostic significance of VPBs in subjects without heart disease[1].

When ambulatory electrocardiography was initially used in small population samples for the evaluation of arrhythmias in healthy people, only trivial VPBs were detected[2-11]. However, when Clarke et al.[12] monitored 86 company employees for 48 h, they discovered that complex ventricular arrhythmias might occur as incidental findings in as many as 12% of healthy people.

Since then more than 1000 healthy adult subjects have had a 24-h ambulatory ECG recorded and figures for the prevalence of most ventricular arrhythmias within this population have been established[13]. Asymptomatic healthy subjects with frequent and complex VPBs were followed up with 24-h ambulatory ECG. The arrhythmias have not hitherto shown any prognostic significance for IHD morbidity and 6-5-year mortality[14].

The present study is the first with an 8-year follow-up of apparently healthy subjects. It was set up to assess the predictive value of frequent or complex VPBs for subsequent occurrence of IHD.

Methods

PATIENT POPULATION

Three hundred and ten volunteers from a retired people's leisure club, senior members of a jogging club and their friends and relatives had a 24-h ambulatory ECG recorded. The subjects were healthy and had never consulted a physician for cardiac symptoms. The examination was postponed if any illness had occurred within the last 3 months. None were taking cardiovascular medication. A 2-min 12-lead ECG had to be normal apart from possible rhythm disturbances, and a biplane chest X-ray had to be without cardiac enlargement or increased vascular markings. A physical examination had to be normal with regard to the cardiovascular system. Subjects with arterial hypertension were excluded. A total of 269 subjects fulfilled these criteria, but nine were excluded due to poor quality ambulatory ECG; this left 260 recordings for detailed analysis[10].

There were 170 men (mean age 53 years) and 90 women (mean age 56 years). Their sex and age distribution is shown in Table 1.

FOLLOW-UP METHODS

It was decided to repeat the physical examination, standard ECG and 24-h ambulatory ECG monitoring approximately 8 years following the initial examination. Information concerning all subjects who had died and the cause of death was obtained from the Danish National Register of Death Certificates, and hospital records were obtained on all who had died in a hospital or been admitted to a hospital with cardiac symptoms. In addition
the subject's family physicians were asked about information when necessary. Particular care was taken to document all symptoms and cardiac events.

STATISTICS

Yates' corrected Chi-square test was used for the two-by-two tables.

Results

CLINICAL CHARACTERISTICS

At follow-up, information about possible cardiac disease since the first examination was available in 237 subjects. Nine were lost to follow-up and 14 who were known to be alive did not respond to our questionnaire. Ten responded to the questionnaire, but because they refused clinical examination were not included in the final analysis. None of them had any history of cardiac symptoms. Twelve subjects had died and cause of death was known in 11 (seven cancer, three sudden cardiac deaths, and one cerebral stroke). One subject had in addition suffered a cardiac arrest but was successfully resuscitated. The underlying heart disease was not known. Satisfactory information concerning cardiac events within the follow-up period was therefore available in 226 subjects.

VENTRICULAR ARRHYTHMIAS

Ambulatory electrocardiography was performed at the time of entry into the study in 260 subjects and the prevalence and complexity of VPBs in the study subjects have previously been detailed. In 5% or less of subjects the frequency or form of VPBs were considered 'abnormal' (Table 2) and their value as potential predictors of subsequent IHD assessed in this follow-up study.

'Abnormal' VPBs of one kind or another occurred in 30 out of 98 subjects within the age group 40-49 years, had an equally high number of VPBs 24 h⁻¹. None of those with IHD had 'abnormal' VPBs compared to only 24 out of 132 (18%) without IHD (P < 0.005) (Table 4). Despite a very low incidence of IHD in our population (6%) the predictive value of a positive test was 20%. In Table 5 the relationship between various types of 'abnormal' VPBs and the occurrence of IHD during follow-up is depicted in order of strongest association. The presence of either VPB triplets, or multiform VPBs, or VPB triplets, or R-on-T VPB was associated with an increased risk of developing IHD. The predictive value of a positive test was 20%.

As previously described, the subject's sex, smoking habits or leisure-time physical activity had no statistically significant effect on the frequency of VPBs.

FOLLOW-UP DATA

During follow-up, cardiovascular disease occurred in 18 survivors including four with arterial hypertension. IHD was documented in 13 subjects (11 men). Five who experienced a myocardial infarction and in one asymptomatic subject the ECG indicated a recent myocardial infarction. Three had typical angina pectoris and one documented Prinzmetal variant angina. One person had a pacemaker implanted due to sinus arrest and two had atrial fibrillation. Among those who had died, IHD was documented in three (two had a myocardial infarction and one a history of angina pectoris). Cancer was the most frequent cause of death, diagnosed in seven. Sudden death occurred in four subjects. A 41-year-old man was successfully resuscitated from cardiac arrest while jogging 6 years after the initial examination without documentation of IHD, and at follow-up clinical examination his cardiovascular system was normal.

In Table 3 the clinical characteristics of the 13 subjects with documented IHD is detailed. Six, or 46%, of those with IHD had 'abnormal' VPBs compared to only 24 out of 213 (11%) without IHD (P < 0.005) (Table 4). Despite a very low incidence of IHD in our population (6%) the predictive value of a positive test was 20%. In Table 5 the relationship between various types of 'abnormal' VPBs and the occurrence of IHD during follow-up is depicted in order of strongest association. The presence of either more than 900 VPBs 24 h⁻¹ or ventricular tachycardia of more than three beats, identified five out of 13 (38%) with IHD. Four out of seven who initially had more than 900 VPBs 24 h⁻¹ had IHD on follow-up; among them only two, out of 98 subjects within the age group 40-49 years, had an equally high number of VPBs 24 h⁻¹. None
Table 3 Clinical characteristics and VPB Pattern at the initial examination of 13 subjects who subsequently developed ischaemic heart disease

<table>
<thead>
<tr>
<th>Number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>VPB pattern</th>
<th>IHD diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 h</td>
<td>MF</td>
</tr>
<tr>
<td>108</td>
<td>41</td>
<td>M</td>
<td>1801</td>
<td>x</td>
</tr>
<tr>
<td>297</td>
<td>41</td>
<td>M</td>
<td>1524</td>
<td>x</td>
</tr>
<tr>
<td>315</td>
<td>45</td>
<td>M</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>195</td>
<td>52</td>
<td>M</td>
<td>1063</td>
<td></td>
</tr>
<tr>
<td>203</td>
<td>53</td>
<td>M</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>170</td>
<td>56</td>
<td>M</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>299</td>
<td>58</td>
<td>M</td>
<td>14</td>
<td>(2 forms)</td>
</tr>
<tr>
<td>155</td>
<td>61</td>
<td>M</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>216</td>
<td>62</td>
<td>F</td>
<td>3</td>
<td>(3 forms)</td>
</tr>
<tr>
<td>215</td>
<td>64</td>
<td>M</td>
<td>42</td>
<td>x</td>
</tr>
<tr>
<td>172</td>
<td>65</td>
<td>F</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>M</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>238</td>
<td>76</td>
<td>M</td>
<td>973</td>
<td>x</td>
</tr>
</tbody>
</table>


Table 4 The relationship between ‘abnormal’ VPBs in the initial recording and IHD at follow-up

<table>
<thead>
<tr>
<th>Ischaemic heart disease</th>
<th>'Abnormal' VPBs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>'Abnormal' VPBs</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

The figures are number of subjects within each group.

Table 5 Incidence of ischaemic heart disease among subjects with various forms of ventricular premature beats in a random 24-h ECG

<table>
<thead>
<tr>
<th>VPB pattern</th>
<th>Number of subjects</th>
<th>% (number) with IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Abnormal' VPB pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 900 VPBs 24 h⁻¹</td>
<td>30</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>7</td>
<td>57 (4)</td>
</tr>
<tr>
<td>Bi, tri- or quadrigeminy</td>
<td>2</td>
<td>50 (1)</td>
</tr>
<tr>
<td>&gt; 200 VPBs 24 h⁻¹</td>
<td>14</td>
<td>29 (4)</td>
</tr>
<tr>
<td>&gt; 2 pairs of VPB episodes</td>
<td>12</td>
<td>17 (2)</td>
</tr>
<tr>
<td>VPB triplets</td>
<td>7</td>
<td>14 (1)</td>
</tr>
<tr>
<td>R-on-T VPB</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>'Normal' VPB pattern</td>
<td>196</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

of the five subjects with either VPB triplets or R-on-T VPBs developed IHD.

Discussion

In studies based upon ordinary 12-lead ECGs it has rarely been possible to show the value of VPBs’ ability to predict subsequent IHD[11], Cullen et al.[11] performing multivariate discriminant analysis of isolated abnormalities in the resting ECG of 1546 subjects (age 40–74 years) with no previous history of angina or myocardial infarction found, however, a significant independent relationship between VPBs and cardiovascular disease. During a 16-year follow-up period, mortality for those with frequent VPB was more than twice the mortality among subjects with infrequent VPBs. Other studies have failed to show such a relationship, and it has been assumed that an ordinary ECG is inadequate for the assessment of VPBs. Based on our own experience[10] the ordinary ECG only identifies 7% of those who have VPBs in the following 24-h period and only 77% of those who have many VPBs. At the same time, 19% of those who have VPBs in the ordinary ECG have only very few in the subsequent 24-h period.

Studies using 24-h ambulatory ECG recordings have failed to show any increased risk of death in healthy adult subjects with frequent or complex VPBs, followed for up to 20 years[12], and this recently led to the conclusion that 'Premature ventricular complexes and even ventricular tachycardia, if detected by ambulatory electrocardiography in asymptomatic patients without organic heart disease, have virtually no predictive value for future cardiac events'[13]. However, by 1961 Pell and D’Alonzo had made the observation that VPBs occurred in the ECG of a significant proportion of workers who subsequently developed acute myocardial infarction[14], and Hinkle et al.[15], who were among the first to use Holter monitoring for an evaluation of the prognostic significance of VPBs in healthy people and in people with coronary heart disease found that the presence of frequent VPBs was evidence of underlying heart disease. More than 10 VPBs 1000⁻¹ QRS or approximately 1000 VPBs 24 h⁻¹ were seen in 16% of subjects with coronary heart disease, compared to only
5% of healthy people. A similar observation was made by Ingerslev and Bjerregaard in 73 subjects aged 85 years\[16\]. More than 1000 VPBs 24 h\(^{-1}\) occurred in their study in 53% of patients with documented IHD compared to only 5% of 22 healthy subjects.

In 1980 Orth-Gomer\[17\] observed that VPBs occurred with the highest frequency in patients with manifest IHD, at an intermediate frequency in subjects with risk indicators of IHD and least frequently in healthy people without such risk factors. Examining the frequency of extrasystoles in healthy male employees, the same group\[9\] found in 1986 that more than 36 VPBs h\(^{-1}\) or 846 VPBs 24 h\(^{-1}\) was only seen in 5% of healthy men above 40 years of age. Kennedy et al. performed cardiac catheterization and coronary angiography in 25 out of 62 asymptomatic subjects aged 21 to 65 years (median 53 years) with frequent VPBs\[18\]. Six (24%) had significant coronary artery disease (\(\geq 50\%\) luminal narrowing), whereas five (20%) had non-critical (<50%) narrowing. Although they concluded: 'the majority of apparently healthy subjects with frequent and complex ventricular ectopy do not have covert non-critical or significant coronary artery disease' it is noteworthy that the 11 subjects with coronary artery disease were found among the 17 subjects above 40 years. Consequently 11 out of 17 subjects (65%) above 40 years with frequent VPBs were shown to have coronary artery disease.

These studies, looking at a possible relationship between high number of VPBs 24 h\(^{-1}\) and IHD, have clearly documented such a relationship and suggested that approximately 1000 VPBs 24 h\(^{-1}\) is a rare finding in healthy subjects and very likely linked to IHD. Our study is, however, the first using 24 h ambulatory ECG recording in concurrently followed populations, one with 'abnormal' VPBs and the other without, that has been performed in order to determine prospectively the predictive value of particular types of VPBs for subsequent IHD.

Our study substantiates previously mentioned reports indicating a favourable survival prognosis in apparently healthy subjects with 'abnormal' VPBs, since only one of our 30 subjects with 'abnormal' VPBs died of cardiovascular disease during an 8-year follow-up.

In contrast, the present study discloses a less favourable association between 'abnormal' VPBs and other clinical manifestations of IHD. The number of VPBs 24 h\(^{-1}\) is the strongest predictor of coronary heart disease, whereas VPB triplets and R-on-T VPBs are not necessarily linked to any heart disease.

In this report, a relatively high number of subjects were either lost from follow-up or excluded due to refusal to appear for physical examination. Despite this apparent limitation our data and conclusions are not hampered since only one patient dropped out who originally had an 'abnormal' 24 h recording and none of the excluded 24 subjects, who did report on their health, had any symptoms of heart disease. Further, no available data on the remaining subjects gave any reason to suspect intervening cardiac disease.

Exercise tolerance test with or without thallium scintigraphy and ambulatory ST-segment monitoring are some of the non-invasive methods currently used for the identification of subjects with IHD. With a diagnostic sensitivity and specificity of 0.38 and 0.98 respectively it would seem reasonable to include 24 h arrhythmia monitoring in the armamentarium for detection of IHD in adult subjects. Combined recording of the ST segment and heart rhythm over a 24-h period may turn out to be more sensitive than isolated recording of either the ST segment or the heart rhythm. Further studies are, however, warranted to confirm our data and to test a combined 24-h ST segment and VPB recording as a valid non-invasive method for identification of subjects with asymptomatic IHD.

This study was supported by the Danish Heart Foundation.

References


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References

mild, contrast in the left ventricle clears with each beat and the ventricle is not fully outlined by contrast; moderate, ventricle fully outlined by contrast but opacification does not equal that of aorta; severe, dense opacification of ventricle equal to that of aorta. At ventriculography, mitral regurgitation was categorized as follows; mild, contrast in left atrium does not fully outline left atrium and contrast clears with each beat; moderate, contrast fully outlines left atrium but opacification does not equal left ventricular opacification; and severe, opacification in left atrium equal to that in the left ventricle.

POST CATHETERIZATION ASSESSMENT

After reviewing the catheterization data, a further written report with gradings of valve severity and management decisions was made by the attending cardiologist. If a management decision differed from that provided before catheterization, the clinician was asked to nominate the major factor which led to the change in management.

STATISTICS

Continuous variables are reported as mean ± standard deviation. Least squares linear regression and the method of Altman and Bland were used to compare echocardiographic and catheterization derived valve areas.

Results

A final recommendation was made for surgery in 78 patients (85%). Management decisions changed after catheterization in nine patients (10%) and did not change in 84 (90%). In four patients a change was made from surgical to medical therapy, and in five patients from medical to surgical therapy. The patients in whom management changed and the reasons for the changes are described below in relation to the involved valve.

AORTIC STENOSIS

There were four patients with isolated aortic stenosis in whom management changed (patients 1, 2, 3 and 4 in Table 3). In one patient (patient 1) this occurred as a result of a small difference between the echocardiographic and catheterization-derived aortic valve areas, although both methods still classified the aortic stenosis as severe. This patient was totally asymptomatic and had normal left ventricular function and coronary arteries. Aortic valve area was measured at 0.61 cm² at echocardiography and at 0.75 cm² by catheterization. This small difference was felt by the clinician to be sufficient reason to change management from surgical to medical.

Patient 2 presented with severe cardiac failure and signs not typical of severe aortic stenosis. Although echocardiography reported severe aortic stenosis on the basis of a valve area of 0.69 cm², the clinician did not believe the patient had severe aortic stenosis and made a recommendation for medical treatment. After catheterization, at which the aortic valve area measured 0.55 cm², this opinion was changed and a recommendation made for surgery.

In patients 3 and 4 management changed as a result of coronary angiography. Both these patients were elderly (aged 84 and 78 years respectively) and were poor operative risks due to associated medical illnesses. In patient 3 the presence of severe diffuse coronary disease, considered inoperable, led to a decision to treat medically while in patient 4 the absence of coronary disease allowed the cessation of negatively inotropic therapy, with subsequent improvement in symptoms.

MITRAL STENOSIS

No management changes were made in the 16 patients with isolated mitral stenosis.

MITRAL REGURGITATION

In two patients, both with concomitant aortic valve disease, management changes resulted from disagreement over the extent of mitral regurgitation. Patient 8, with moderate degenerative aortic stenosis was assessed as having only minimal additional mitral regurgitation at the non-invasive assessment. However, catheterization demonstrated moderate mitral regurgitation and aortic and mitral valve replacements were recommended. In a further patient with aortic stenosis (patient 9), precatheterization assessment reported moderate mitral regurgitation but at ventriculography only mild mitral regurgitation was seen, and only aortic valve replacement was recommended.

AGREEMENT BETWEEN ECHOCARDIOGRAPHY AND CATHETERIZATION

There were 40 patients with aortic stenosis in whom measurement of aortic valve area was possible by both echocardiography and catheterization. Patients with moderate or severe aortic regurgitation at angiography were excluded from this comparison. The regression equation predicting catheter area from echocardiographic area was 

\[ y = 0.17 + 0.66x, r = 0.86, \text{standard error of the estimate } 0.19 \text{cm}^2. \]

Agreement between the two methods analysed by the method of Altman and Bland is shown in Fig. 1.

There were 26 patients with mitral stenosis in whom measurement of mitral valve area could be made by
Mean aortic valve area by the two techniques (cm$^2$)

Figure 1 Agreement between echocardiographic and catheterization-derived aortic valve areas in the patients with aortic stenosis. In this plot, the horizontal axis displays the mean value for the two measurements for each patient and the vertical axis, the difference between the two measurements for each patient. The solid line indicates the mean value for the differences between the two measurements and the dashed lines, 2 standard deviations from this mean. The mean is close to zero indicating no bias in the measurements, but there is moderate error with the 95% range of differences from 0.57 to $-0.43$ cm$^2$.

Mean mitral valve area by the two techniques (cm$^2$)

Figure 2 Agreement between echocardiographic and catheterization-derived mitral valve areas in the patients with mitral stenosis. Figure arranged as in Fig. 1. There is significant overestimation of mitral valve area by echocardiography as compared to catheterization and a large amount of error.

echocardiography and catheterization. Patients with moderate or severe mitral regurgitation at aortography were excluded from this comparison. The regression equation was $y = 0.27 + 0.89x$, $r = 0.65$, standard error of the estimate $0.43$ cm$^2$. Agreement between the two methods is shown in Fig. 2.

Agreement between the semiquantitative echocardiographic and catheterization gradings of mitral and aortic regurgitation are shown in Figs 3 and 4. Overall, there was agreement in 67% of comparisons, disagreement by one grade in 32% and disagreement by two grades in 1%.

Discussion

In this study we wished to determine how often the additional information obtained from cardiac catheterization altered management decisions in patients with advanced valvular disease being considered for surgery. We found that intended management changed in only nine of the 93 (10%) patients and did not change in the remaining 84 (90%).

In three patients (patients 5, 8 and 9 in Table 3) management changed as a result of clear differences between echocardiographic and catheterization assessment of valve lesion severity, and in each case, differences occurred in the assessment of valvular regurgitation. All three patients had both aortic and mitral valve disease. These management changes demonstrate that, although there is reasonable overall agreement between echocardiography and catheterization, serious errors may still occur in the assessment of valvular regurgitation by echocardiography. In view of the limitations of Doppler echocardiography in assessing valvular regurgitation$^{12}$, catheterization should usually be performed before operation in patients with
valvular regurgitation, particularly when multiple valves are diseased and when any clinical uncertainty exists.

The correlation observed between echocardiographic and catheterization assessment of mitral valve area in this study was worse than some previous reports. The limitations of using pressure half-time to measure mitral valve area have recently been appreciated. Nevertheless, management changes did not result in patients with isolated mitral stenosis. The reasons for this are uncertain, but may reflect in part the younger age and lower prevalence of coronary disease and other medical illnesses in patients with mitral stenosis.

Coronary angiography influenced the decision to undertake valve surgery in two elderly patients with aortic stenosis. That coronary angiography was responsible for management changes in only a small number of patients was not unexpected since the presence or absence of coronary disease in itself, would be considered unlikely to alter the decision to operate upon a valve. Nevertheless, coronary angiography would still be required in many patients before operation in order to determine the extent of coronary disease, irrespective of the need for haemodynamic evaluation of valvular disease. Avoidance of detailed haemodynamic studies, however, may considerably shorten the time required for catheterization and lessen the risk of the procedure.

In this study we did not prospectively assess the confidence of the clinician's decision before catheterization. Others have shown that this is an important factor in assessing management decisions before operation. However, it is possible to infer that six of the nine patients in whom management changed (those where information on coronary anatomy or small or no changes in assessment of valvular severity led to management changes) may have been among those where clinical uncertainty existed and where the clinician would have preferred to have catheterization information available before making a final management decision.

One limitation of this study is the absence of a gold standard for the pre-operative evaluation of valvular heart disease. Therefore, it is difficult to determine if the management changes in this study were ultimately beneficial to our patients. This would require a different trial design with large numbers of patients and prolonged follow-up, due to logistic and ethical difficulties such a trial is unlikely to be performed.

Nevertheless, in a large majority of patients, a combination of clinical and noninvasive assessment including Doppler echocardiography, resulted in a reliable evaluation of valvular disease, when compared to cardiac catheterization. Thus, pre-operative cardiac catheterization for haemodynamic assessment can be reserved for selected patients with either complex valvular disease or those in whom clinical uncertainty exists after clinical and non-invasive assessment.

References