Improved Classifications of Myocardial Bull's-Eye Scintigrams with Computer-Based Decision Support System

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In a recent study, artificial neural networks were trained to detect coronary artery disease using scintigraphic data as input. The performance of the networks was better than that of human experts using coronary angiography as a gold standard. In clinical practice, this type of neural networks will not take over the decision-making process from the physician but will assist by proposing an interpretation of the scintigram. The purpose of this study was to assess the influence of such decision support on the interpretations of the physicians. **Methods:** A population of 135 patients who had undergone both myocardial ^{99m}Tc-sestamibi rest/stress scintigraphy and coronary angiography within a 3-mo period was studied. An image set consisting of the bull's-eye rest, stress, difference and quote images was constructed for each patient. Three experienced physicians independently classified all image sets regarding the presence and/or absence of coronary artery disease in two vascular territories using a four-grade scale. The physicians classified the image sets twice with and twice without the advice of artificial neural networks. **Results:** The joint evaluation of the three physicians showed significantly improved performance with decision support, measured as increases in the areas under the receiver operating characteristic curves from 0.65 to 0.70 ($P = 0.018$) and from 0.79 to 0.82 ($P = 0.006$) for two vascular territories. Furthermore, the joint evaluation showed significantly less intraobserver and interobserver variability with decision support. **Conclusion:** Physicians classifying myocardial bull's-eye images benefit from the advice of artificial neural networks. These results show the high potential for neural networks as clinical decision support systems.

Key Words: artificial intelligence; computer-assisted diagnosis; ischemic heart disease; radionuclide imaging

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Interpretation of diagnostic images is to a great extent a pattern recognition task. Physicians must rely on their experience rather than on simple rules of how to interpret the image. Artificial neural networks are computer-based decision support tools that also rely on experience from a learning procedure, and they have proved to be of value in pattern recognition tasks (*1*). There are many neural network applications in the medical field (*2,3*), and four reports have presented networks that classify myocardial perfusion scintigrams (*4–7*). The usefulness of such neural networks as clinical decision support systems has to be evaluated, and in the first stage, the performance of a system has to be established against an objective gold standard. One recent study showed that the performance of the neural networks trained to detect coronary artery disease in myocardial bull's-eye scintigrams was better than that of two experienced experts who independently classified the same images using coronary angiography as a gold standard (*7*). These results provide a platform for further evaluation of these neural networks.

In clinical practice, this type of neural networks will not take over the decision-making process from the physician. The computer could assist the physician by proposing an interpretation of the scintigram. Therefore, the second stage in the evaluation of the neural networks was focused on how the networks alter the decisionmaking of physicians. Classifications of myocardial perfusion bull's-eye scintigrams made independently by three physicians were evaluated in this study. The physicians classified all bull's-eye scintigrams both with and without the advice of the neural networks. The purpose of this study was to assess the influence of the neural networks on the classifications of the physicians with respect to intraobserver variability, interobserver variability and performance.

MATERIALS AND METHODS

Patient Population

All patients at Lund University Hospital who, during the period from November 1992 to October 1994, had undergone both rest/stress myocardial perfusion scintigraphy and coronary angiography, with no more than 3 mo elapsing between the two examinations, and who had not undergone coronary artery bypass surgery were studied retrospectively. There were 166 such patients, 31 of whom were excluded because they had undergone angioplasty or had signs of progressive coronary artery disease between the scintigraphy and the angiography. The population studied consisted of the remaining 135 patients (94 men and 41 women), who had a mean age of 56.7 y (range, 21–77 y). In 55 patients, the angiography examination was performed before the scintigraphy. A

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contrast left ventriculogram was performed in 106 patients. The ejection fraction was normal in 65 patients (61%), slightly to moderately reduced in 28 patients (26%) and severely reduced in 13 patients (12%).

Coronary Angiography

Coronary angiography was used as a gold standard. The patients were examined using the standard Judkins' technique. Angiograms were performed and interpreted by experienced cardiac radiologists. Each coronary artery was examined in four to six projections, of which at least two were orthogonal. Significant coronary artery disease was defined as ≥75% reduction of the lumen area in a major coronary artery. The severity of a coronary stenosis was determined by visual assessment.

The total myocardial perfusion bed was divided into two vascular territories. One territory was assigned to the vascular bed of the left anterior descending artery (LAD); the other territory was assigned to the vascular bed of the left circumflex artery (LCX) and the right coronary artery (RCA) together. Each territory was studied separately regarding presence or absence of coronary artery disease. In 41 patients, coronary artery disease was found in both the LAD and the RCA/LCX territories, and in 46 patients, coronary artery disease was found in one territory only (15 in LAD and 31 in RCA/LCX). Coronary angiography did not show significant coronary artery disease in the remaining 48 patients.

Myocardial Scintigraphy

Rest and stress studies were performed in a 1-d SPECT ^{99m}Tc-sestamibi protocol using 300 MBq at rest and, after a delay of about 3 h, 900 MBq under stress. Of the 135 patients studied, 131 exercised on a bicycle ergometer, and 4 were injected with 0.56 mg/kg dipyridamole. Exercise was symptom limited (anginal pain, severe dyspnea or severe fatigue) unless malignant arrhythmia or exercise hypotension occurred (>10 mm Hg decrease between exercise stages). Work load was increased in a stepwise manner by 10 W/min.

The scintigraphy data were acquired in continuous SPECT over 180° during 20 min with a gamma camera (GCA-901A/SA; Toshiba Corporation, Tokyo, Japan). The data-processing technique has been described in detail elsewhere (*7*). A short-axis slice set was generated for entry into a bull's-eye program, in which careful three-dimensional alignment of the rest and stress images was performed on an interactive basis by experienced clinical operators. This procedure included translations along the left ventricle axis and small corrections to the initially selected direction of this axis. Rotations about the axis were not made. After slice selection and positioning, data were sampled for the myocardial maximum in 64 radial directions for each slice, including the apex. The sampled data were then interpolated linearly to exactly 17 slices and organized in a matrix map of size 17 slices × 64 angles. The rest matrix, corrected for decay of ^{99m}Tc during the interval from rest to stress, was subtracted from the stress matrix as background. The maps were then normalized as follows: the rest map was scaled such that the average value of the region above 90% of its maximum was put to a fixed value, which was the same for all patients. The stress map was then scaled such that its average value, in the region above 90% of its maximum, was made equal to the average value of the rest map in a geometrically identical region. This normalization makes the rest and stress data equal in a region that is likely to be least ischemic and makes the absolute normalization dependent on the rest data only.

Artificial Neural Network Input Data

To shrink the dimensionality of the artificial neural network input space, a two-dimensional Fourier transformation was applied to the bull's-eye scintigrams. SPECT bull's-eye image data were taken as the start values, and image data reduction was performed using the two-dimensional Fourier transformation as described by Lindahl et al. (*7*). In short, the rest and stress images served as input as the real and imaginary parts of a complex matrix to a fast Fourier transformation. Thirty values describing the lowest of the resulting frequency components were chosen to represent the bull's-eye images. With this technique the bull's-eye data were reduced to 30 values without losing diagnostically important information (*7*).

Artificial Neural Networks

The same artificial neural networks were used in this study as in a previous one (*7*). In short, a multilayer perceptron neural network architecture (*8*) was used. The networks consisted of one input layer one hidden layer and one output layer. The number of neurons in the input layer was equal to the number of input variables, i.e., 30. The hidden layer contained three neurons, and the output layer contained one neuron that encoded whether or not coronary artery disease was present. Two different sets of networks were studied: one that detected coronary artery disease in the LAD territory and one that did so in the RCA/LCX territory. The same network architecture and training parameters were used for all of the networks.

During the training process, the connection weights between the neurons were adjusted using the back-propagation algorithm (*8*). The sigmoid activation function was used. The learning rate had a start value of 0.3. During the training, it was decreased between epochs. The momentum was set to 0.7. The network weights were initiated with random numbers between −0.03 and 0.03. The network training was stopped when the error in the training set reached 0.36. This error threshold was decided using a threefold cross-validation procedure. In the final training procedure, a "leave-one-out" validation procedure was used. One patient study was used as a test case, whereas the remaining 134 patients were used for training. This procedure was repeated 135 times such that each case in the data set was used as a test case once. The test results of the 135 different networks were then concatenated, and the resulting list was used as the basis for the decision support system. All calculations were done using the JETNET 3.0 package (*9*). The performance of the networks on this particular material was 0.76 (in LAD) and 0.82 (in RCA/LCX), measured as areas under the receiver operating characteristic (ROC) curves (*7*).

Classification of Physicians

The physicians' classified image sets consisted of the following four bull's-eye images: the rest image, the stress image, the difference image and the quote image (Fig. 1). Neither short- or long-axis images nor quantitative analysis images, such as CEqual, were used (*10*). The difference image showed rest minus stress. The quote image showed the quote between stress (numerator) and rest (denominator). This set of four images has been used at the clinic for a long time, and the physicians were well acquainted with the images.

The classifications of three physicians were studied. The physicians had 1, 3 and 20 y of experience in interpreting myocardial scintigrams. They are referred to in the text as physicians 1, 2 and 3, respectively. They classified the image sets regarding the presence or absence of coronary artery disease in the two vascular territories

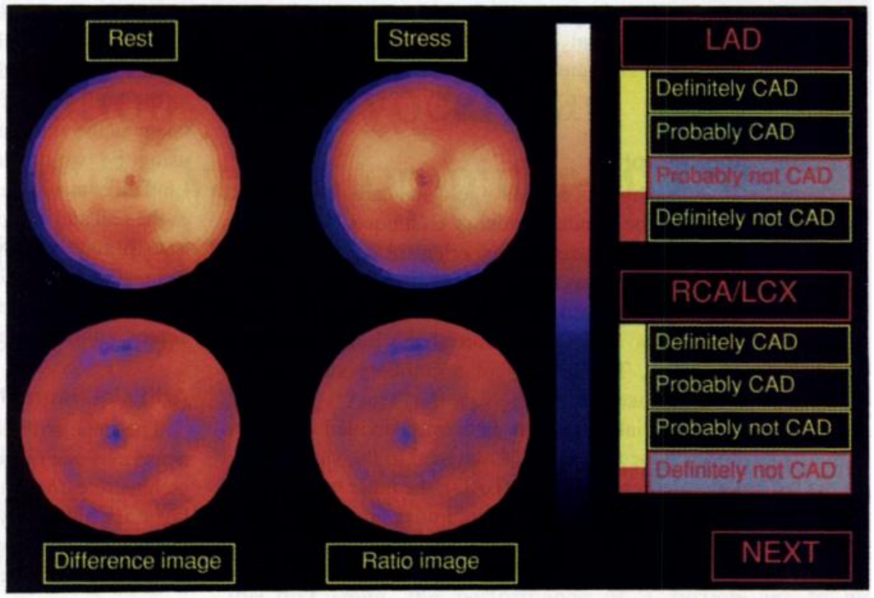

FIGURE 1. Computer screen with set of four bull's-eye images and four buttons each for LAD and RCA/LCX classifications. Advice of the decision support was presented to physicians as preselected buttons. Neural network output values were indicated using two vertical thermometer-like scales (to left of buttons). This patient did not have coronary artery disease.

using a four-grade scale: C1, definitely not coronary artery disease; C2, probably not coronary artery disease; C3, probably coronary artery disease; and C4, definitely coronary artery disease.

The classifications were made in a blinded fashion, in other words, the image sets were presented to the physicians without any clinical data, results from angiography, or classifications of the other physicians. Each physician classified the image sets four times. In a first session, each image set was classified twice without the aid of decision support. In a second session each image set was classified twice with the aid of the computer-based decision support. In each session, the 270 image sets were presented in random order with one exception: there had to be at least 10 image sets between the two identical image sets from the same patient.

Computer-Based Decision Support

The output values of the network were ranged from 0 to 1. Three thresholds were used to transform the output values into the four-grade scale used by the physicians. For example, output values below the lowest threshold were regarded as "definitely not coronary artery disease." The thresholds were selected to give the same number of scintigrams in each of the four groups, as was the case for two experts (none of them were among the three physicians) who blindly and independently classified the same image sets. The results of the classifications of the two experts have been presented previously (*7*).

The image sets were presented to the three physicians on a computer screen as shown in Fig. 1. The physicians made their classifications by clicking on the appropriate buttons on the screen. During the classification sessions "with decision support," one of the four buttons for the LAD classification and one of the four buttons for the RCA/LCX classification were preselected. If the physician agreed with the classification of the neural network, he just clicked on the "next" button. Otherwise, he clicked on the classification buttons of his choice. Furthermore, the actual output values were indicated using two thermometer-like scales. During the classification sessions "without decision support," the preselection and indication of network outputs were not shown on the computer screen. The physicians were not told to use any explicit rules on how to use the network support.

The influence of the computer-based decision support system on the classifications of the physicians was analyzed from the following three points of view: intraobserver variability, interobserver variability and performance. All analyses described below were performed twice: once for the LAD data and once for the RCA/LCX data.

In the analysis of intraobserver and interobserver variability, the difference between two classifications made on the same image set was assessed using an ordinal scale as follows: large disagreement, C1 versus C4; medium disagreement, C1 versus C3 and C2 versus C4; small disagreement, C1 versus C2, C2 versus C3 and C3 versus C4; and no disagreement, C1 versus C1, C2 versus C2, C3 versus C3 and C4 versus C4. This implies that there was no differentiation inside each group, i.e., a difference between C1 and C3 was assessed in an equally severe manner as a difference between C2 and C4.

Intraobserver Variability

The influence of the decision support on intraobserver variability for one physician was assessed as follows. For each image set, the difference between the two classifications made with decision support was compared with the difference between the two classifications made without such support. The number of cases with a less severe disagreement with decision support was compared with the number of cases with a less severe disagreement without decision support. The significance of an imbalance in these numbers was evaluated using a McNemar type of statistics.

To obtain a joint evaluation for the three physicians together, the following reasoning was used.

1. If more physicians had less severe disagreement with decision support, that image set was said to vote for "with decision support" and vice versa.
2. If one physician had a less severe disagreement with decision support, one had a less severe disagreement without decision support and one had equally severe disagreements with and without decision support, the image set voted for "with decision support" if the first physician had a greater disagreement between the two support levels than the second physician, and vice versa.
3. In all other cases, the image set abstained from voting.

The number of votes for "with" and "without" decision support was counted. The significance of an imbalance in these numbers was evaluated using a McNemar type of statistics.

Interobserver Variability

It was possible to form three pairs of physicians. The influence of the decision support on interobserver variability for one pair was considered as follows. For each scintigram, the two physicians made two classifications each without support. Four different pairs of classifications, in which each pair consisted of one classification from each physician, were analyzed. The four classification differences were ordered in order of severity. Similarly, the four classification differences between the two physicians with decision support were ordered by severity. If all four differences with support were equal or less than the differences in the corresponding position without support and with strict inequality in at least one position, the image set was said to vote for "with decision support" and vice versa. In all other cases, the image set abstained. The number of votes for "with" and "without" decision support was counted. The significance of an imbalance in these numbers was evaluated using a McNemar type of statistics.

To obtain a joint evaluation for the three pairs of physicians the following method was used. By analogy with the previously described method, 12 differences between the physicians (four differences for each of the three pairs) without decision support were ranked in order of severity, and the same was done with the 12 differences with decision support. If all 12 differences with support were equal or less than the differences in the corresponding position without support and with strict inequality in at least one position, the case was said to vote for "with decision support" and vice versa. In all other cases, the image set abstained. The number of votes for "with" and "without" decision support was counted. The significance of an imbalance in these numbers was evaluated using a McNemar type of statistics.

Performance

The four-grade scale used for classification of the scintigrams made it possible to calculate three sensitivity/specificity pairs. These three pairs were used to construct a ROC curve, and the area under the curve was used as a measure of the performance. A difference in the ROC area would point out that adding decision support would alter the performance of the interpreting physician. For each of the three physicians, two ROC curves were constructed: one using classifications with decision support and one using classifications without decision support. The difference in performance between with and without decision support was measured as the difference in area under the ROC curves. The significance of such an area difference was calculated using the Monte Carlo technique as follows.

A new classification list was created by randomly selecting for each of the 135 scintigrams either the two classifications made with support or the two classifications made without support. A second list was created from the classifications not included in the first one. The two lists were used to construct two ROC curves, and the areas under the curves were calculated, as was the area difference. The procedure was repeated 1000 times. The relative frequency of area differences that had an absolute value greater than the actual difference was taken as the probability of obtaining at least the actual area difference if no true difference existed.

To obtain a joint evaluation for the three physicians, all six classifications (three physicians, two classifications each) made with decision support were used to construct a ROC curve. Another ROC curve was constructed for the classifications without decision support. The difference in performance with and without decision support was measured as the difference in area under the ROC curves. The significance of such an area difference was calculated using the same technique as for the individual physicians, i.e., by creating a new classification list by selecting for each scintigram either the six classifications made with decision support or the six classifications made without decision support.

RESULTS

The physicians classified each of the 135 scintigrams twice without decision support, and in 28% of the cases, they made two different classifications for the same scintigram. With the advice of the networks, this figure decreased to 18%, indicating an improved consistency of the physicians.

The assessment of intraobserver variability using the method described above showed that two of the physicians classified significantly more cases with less variability using decision support in the LAD area. In the RCA/LCX area, one physician classified significantly more cases with less variability using decision support. No physician classified significantly more cases with less variability without decision support, regardless of territory. Both in the LAD and RCA/LCX classifications with decision support, the joint evaluation of the three physicians showed significantly more cases with less intraobserver variability (Table 1).

For physicians 1 and 3, interobserver variability was significantly less with decision support both in the LAD and RCA/LCX classifications; the same applied to physicians 2 and 3. The variability between physicians 1 and 2 was slightly but not significantly less when they used decision support. Also in the joint evaluation, the interobserver variability was significantly less with decision support (Table 2).

In the RCA/LCX classifications, two physicians performed significantly better with decision support, whereas the third and most experienced physician performed slightly but not significantly better with support, measured as an increase in the areas under the ROC curves. In the LAD classifications, one physician performed significantly better with decision support, whereas the two others performed

TABLE 1
Intraobserver Variability: Number of Votes Cast With Versus Without Decision Support

	LAD		RCA/LCX	
Physician	With/ without	*P*	With/ without	*P*
1	36/16	0.0078	23/14	0.19
2	22/15	0.32	26/6	0.00054
3	41/14	0.00036	26/19	0.37
Joint	56/24	0.00045	45/21	0.0043

Significance according to McNemar type of statistics (n = 135).
LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery.

TABLE 2
Interobserver Variability: Number of Votes Cast With Versus Without Decision Support

	LAD		RCA/LCX	
Physicians	With/without	*P*	With/without	*P*
1 and 2	39/33	0.56	34/22	0.14
1 and 3	65/20	0.0000010	51/17	0.000044
2 and 3	52/22	0.00064	43/24	0.027
Joint	64/25	0.000043	54/20	0.000096

Significance according to McNemar type of statistics (n = 135).
LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery.

slightly but not significantly better with decision support. Both in the LAD and RCA/LCX classifications, the joint evaluation of the three physicians showed a significantly improved performance with decision support (Table 3).

The best performance with decision support was achieved by the two physicians (1 and 3) who accepted the suggestions of the network in 78% and 74% of cases, respectively. Physician 2 did not accept the suggestions of the network as often as the other physicians (61%), and his performance with decision support was slightly worse than the others.

DISCUSSION

Main Findings

The aim of this neural network project was to enhance the effectiveness of clinical decision making, not to replace physicians with computers. The results of this study clearly show that even a very experienced physician can benefit from a computer-based decision support system. The most experienced of these three physicians improved his performance slightly but not significantly, and he had significantly less variability in the LAD classifications with decision support. In the classification session without decision support, the most experienced physician showed the best performance, as could be expected. Surprisingly, the best performance using decision support was that of the physician with least experience. A less-experienced physician will probably rely more on a decision support system than will an experienced colleague. However, there were three physicians, each representing a certain experience level. The number of physicians has to be increased to obtain more reliable data on how decision support affects physicians with different experience levels. There will also be more factors influencing the way each person uses decision support, and maybe rules on how to use the decision support should be applied for such support to minimize interpersonal differences.

TABLE 3
Physicians' Classification Performance Measured as Areas Under the Curves of Receiver Operating Characteristics: Comparison Between Without Decision Support and With Decision Support

	LAD			RCA/LCX		
Physician	Without	With	*P*	Without	With	*P*
1	0.65	0.72	0.010	0.79	0.84	0.009
2	0.65	0.68	0.17	0.78	0.81	0.027
3	0.67	0.70	0.19	0.79	0.81	0.262
Joint	0.65	0.70	0.018	0.79	0.82	0.006

For Monte Carlo values, see performance section (n = 135).
LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery.

In both the LAD and RCA/LCX classifications, the physicians benefited from the decision support. The three physicians improved their performance with decision support as much in the LAD as in the RCA/LCX classifications. The intraobserver variability was significantly less in the LAD classifications for two physicians, whereas the third physician had significantly less variability in the RCA/LCX classifications. These differences could be because of different opinions regarding the borders of the two vascular territories. It should be stressed that no guideline for assigning a perfusion defect to a specific coronary artery was used in the study. The networks learned to differentiate between coronary artery disease in the LAD and RCA/LCX territories simply by analyzing the examples of the training set, whereas the physicians had to rely on their clinical experience.

Clinical Implications

Modern computer technology has made it possible for physicians to retrieve diagnostic images, as well as clinical data from computer-based patient records and results of laboratory tests, to the same computer screen in the clinic, ward or office. With this kind of infrastructure, computer-based decision support systems can be of great value. The computer's advice can easily be presented together with other information. A common feature of computer-based decision support systems is the tradeoff between accuracy and transparency. Artificial neural networks have been shown to be highly accurate in several applications (*2,3*), and they have outperformed more transparent rule-based criteria (*11,12*). The disadvantage of the neural networks is their inability to present meaningful explanations of their advice. However, humans interpret images intuitively, and, therefore, there is often little need for explanations. Indeed, humans cannot explain the procedures they use for vision recognition. Using a very accurate but not very informative neural network for image interpretation would therefore be acceptable for most users. It could be more difficult to rely on a neural network diagnosing acute myocardial infarction based on clinical findings, as investigated by Baxt and Skora (*13*).

Future Evaluations

The long-term goal for the development of decision support systems is to show a positive effect on clinical care. This report presents only an intermediate evaluation of an artificial neural network trained to classify myocardial perfusion bull's-eye scintigrams. The next stage in the evaluation process of these networks will be to test them in a setting away from the department in which they have been developed. Widespread use of these networks can be expected only if they can perform well in clinical settings with, e.g., different patient populations and different protocols for image acquisition.

Limitations of the Study

Our aim with this study was to investigate whether or not physicians benefit from the advice of a decision support system. The physicians were told to interpret the myocardial scintigrams regarding the likelihood of coronary artery disease only. This gave us the opportunity to use coronary angiography as an independent gold standard. We have shown in a recent study that this task can be solved by analyzing the bull's-eye images only (*14*). In that study, the physicians were not able to assess the likelihood of coronary artery disease more accurately when tomographic long- and short-axis images were presented to them in addition to the bull's-eye images. Therefore, only bull's-eye images were used in this study. In the clinical routine, physicians interpret scintigrams also regarding, e.g., presence or absence of ischemia, and in this situation, physicians use all available information, i.e., also tomographic long- and short-axis images.

In this study, we divided the myocardial perfusion bed into two vascular territories instead of the conventional three, and this approach has been used also by others (*5*). However, a neural network could be trained to also give suggestions other than the probability of coronary artery disease in the LAD and RCA/LCX territories. It could, for example, be of clinical interest to use neural networks that analyze the myocardial scintigrams regarding ischemia and infarction or one-, two- and three-vessel disease.

The ordinal scale used to order the amount of disagreement between classifications could be both a strength and a weakness of the study. The strength is that the scale gives a means to identify even small improvements in variability, e.g., from "medium" to "small" disagreement, compared with a binary scale (agreement and disagreement). The weakness is that, if, for example, a disagreement between C4 and C3 is assessed as worse than a disagreement between C3 and C2, the scale may affect the variability conclusions reached.

CONCLUSION

Physicians interpreting myocardial perfusion bull's-eye scintigrams benefit from the advice of artificial neural networks. These results show the high potential for neural networks as clinical decision support systems.

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