Interpretation of Captopril Transplant Renography Using a Feed Forward Neural Network

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Severe renal artery stenosis (RAS) is a relatively uncommon complication after renal transplantation but is a curable cause of hypertension, which demands reliable early diagnosis to reduce morbidity, mortality and graft loss. Captopril renography has been used for a number of years as a method of detecting RAS but controversy still exists as to the diagnostic accuracy of this test and as to the most appropriate interpretation criteria with which to establish a positive result. **Methods:** This report presents the results of using artificial neural networks to impartially assess these interpretation criteria. Data comprised 31 ^{99m}Tc-MAG3 captopril renography investigations undertaken on hypertensive renal transplant patients with a suspected diagnosis of RAS. Each renogram study was correlated with an arteriogram as the "gold standard". Training of the network was performed using the round-robin technique. **Results:** An accuracy of 95% could be achieved by considering perfusion index, time-to-peak activity, accumulation index and excretion index for both pre- and post-challenge studies. This varied as the parameters were either included or excluded. **Conclusion:** Artifical neural network analysis is a useful technique to evaluate the most appropriate criteria for interpreting captopril transplant renography investigations.

Key Words: neural network; captopril; renography; transplant; MAG3

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Severe renal artery stenosis (RAS) leading to hypertension or impairment of renal function in transplant patients is relatively uncommon (*1*), but it is a potentially curable entity in which early diagnosis and appropriate treatment can reduce morbidity, mortality and loss of graft. There are several methods of detecting RAS, but angiography remains the "gold standard" (*2,3*). This is an invasive technique, however, and one which is potentially dangerous to graft function. An alternative is the captopril renogram test (CRT) which has been used since 1983 (*4*) as a noninvasive investigation to diagnose functionally significant RAS in renovascular hypertensive patients. Most of the published data deal with stenoses in patients with native kidneys and only a few institutions have investigated the role of CRT in the diagnosis of transplant renal artery stenosis (TRAS) with results available from only a small number of patients (*2,3,5–7*). Controversy still remains as to the diagnostic value of the test and as to the most appropriate interpretation criteria with which to establish a positive result (*2,8–12*). We recently introduced an additional interpretation criterion of a consideration of the perfusion change between pre- and post-challenge studies which resulted in an improvement in specificity (*13*). We have now extended this work to take advantage of impartial interpretation afforded by artificial neural networks.

Artificial neural networks form a branch of artificial intelligence which has experienced rapid development since the middle 1980s (*14–17*). They are computer systems which can be trained to recognize similarities in patterns and which learn by example (*18,19*). One of the more straightforward types of artificial neural networks is the feed forward neural network (FFNN), which is a fully connected network of neural nodes arranged in input, hidden and output layers shown in Figure 1.

We have previously reported the use of FFNNs for classification of hypoperfusion patterns in bull's-eye representation of ^{201}Tl SPECT myocardial perfusion studies (*20,21*). We have now used FFNNs to impartially assess the interpretation criteria for use in establishing a positive CRT test and have used these criteria to assess the accuracy of the CRT for the diagnosis of TRAS.

MATERIALS AND METHODS

The study comprised 31 CRT investigations with corresponding angiograms undertaken on hypertensive renal transplant patients with a suspected diagnosis of TRAS. Renography was performed after a bolus administration of 200 MBq ^{99m}Tc-MAG3, with the patient supine under a small field of view IGE 300a gamma camera fitted with a low-energy, general-purpose, parallel-hole collimator. Sixty 1-sec frames and eighty-seven 20-sec frames were acquired on a 64 × 64 matrix. The investigation protocol consisted of a baseline study followed by a second study performed on a following day 1 hr after oral administration of 50 mg of captopril. ACE inhibitors and diuretics were stopped at least 3 days before the initial study and until after the second study (*8*). The patients remained well hydrated.

For both the pre- and post-challenge studies: the Guy's Perfusion Index was calculated from the perfusion phase according to the method of Hilson (*22*) and renogram activity-time curves were generated. Values of time-to-peak activity, accumulation index (background corrected activity at 3 min) and excretion index (ratio of the activity at 3 min to the activity at 20 min) were calculated from the renogram curves. Each of the 31 investigations was categorized into: true-positive, false-positive, true-negative and false-negative by correlating the CRT result with the angiogram. As previously described (*13*), a CRT result was classed as positive if either excretion index decreased or time-to-peak activity increased and the Guy's Perfusion Index decreased between pre- and post-challenge studies. There were 22 true-positives and true-negatives giving an accuracy of 71%, which is similar to previously reported figures (*2*).

For FFNN analysis, the values of the four parameters obtained from the post-challenge curve were normalized to a corresponding pre-challenge value of 100 and used as input values. These are shown for each of the 31 CRT investigations in Table 1. This procedure was required because it was found that the network could not converge when the raw pre- and post-challenge values were presented as inputs to the network.

The network was trained on unambiguous data, i.e., only on the true-positives and true-negatives. Its ability to extract reliable information was then examined by testing it on both this restricted

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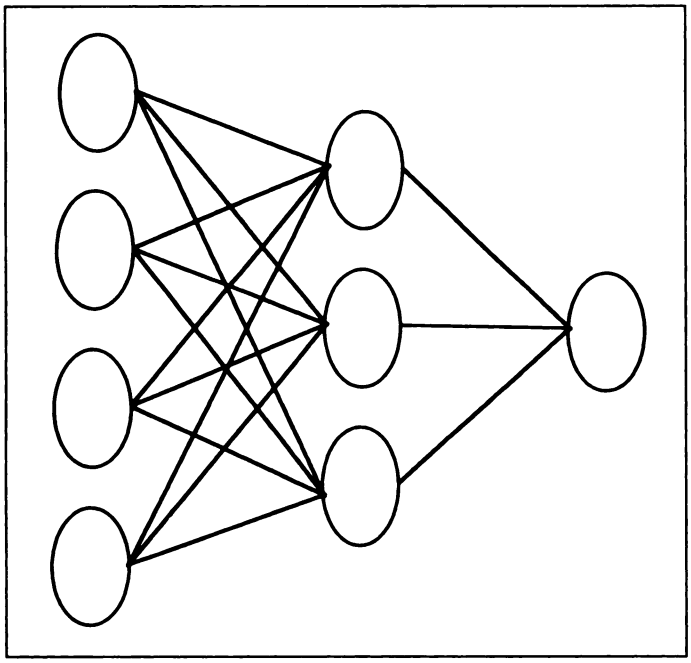

FIGURE 1. A three-layer artificial neural network showing the nodes as ellipses and the connecting weights as lines. The input, hidden and output layers are shown from left to right.

data and subsequently on all datasets. The network was tested to establish which parameters were necessary for accurate interpretation by undertaking the above analyses firstly using all four parameters as input and then by removing one parameter in turn so that it was only trained and tested on three input parameters.

The input layer of the network consisted of nodes representing each of the normalized input parameters. The output layer of the network consisted of a single node whose value represented the likelihood of the renal artery being stenosed. During training, this output value was coded as 0.99 when the angiogram showed a stenosis in the renal artery greater than 50% or as 0.01 when the angiogram did not demonstrate significant stenosis. There were three nodes in the hidden layer.

The network was trained using the stochastic backprojection learning rule with a terminating condition of 0.1 maximum error. The network was trained and tested using the round-robin method. According to this method, all patterns but one are used to train the network and the trained network is then tested on the pattern left out. The process is repeated so that every pattern is left out once. This process overcomes the problems associated with limited data. It utilizes the full potential of the available data for training without sacrificing the statistical significance of the testing phase (*23*). For testing the data patterns in the false-positive and false-negative categories, all of the training data sets were used.

The performance of the FFNN for each analysis category was assessed on the basis of receiver operating characteristics (ROC) analyses (*24*), in which the area under the ROC curve was used as the figure of merit (*25–27*). This and the s.e. have recently been suggested as a reliable, robust and unbiased means with which to evaluate the performance of neural networks (*27*). The ROC curves were constructed by determining pairs of true-positive-ratio and false-positive-ratio at threshold values of 0.1, 0.3, 0.4, 0.5, 0.6, 0.7 and 0.9 (*25*). The area under the ROC curves and the s.e. were calculated using the Wilcoxon statistic computational method described by Hanley and McNeil (*26*). The accuracy of the network in each input parameter exclusion category was compared to that in the category which included all four input parameters by calculating the z score and assessing its magnitude relative to the significance value for a two-tailed test (*27*).

TABLE 1
Values of the Four Parameters (PI, TP, AI, EI) Calculated from Post-Challenge Perfusion and Renogram Curves in Each of the Four Classification Categories*

Category	PI	TP	AI	EI
True-positive	38	400	122	37
	59	288	86	87
	46	200	154	79
	44	180	140	61
	68	188	104	71
	64	499	100	32
	83	114	133	102
	60	91	107	91
	95	128	85	129
	43	112	90	290
False-positive	82	143	114	98
	96	120	112	83
	29	282	79	52
	63	150	107	53
	95	192	132	69
	90	550	165	63
True-negative	107	100	65	151
	34	100	133	117
	60	85	117	115
	77	52	143	158
	41	100	84	131
	67	100	133	119
	38	100	130	114
	51	77	85	130
	176	432	69	57
	58	28	132	101
	76	63	91	124
	165	309	116	47
False-negative	32	47	175	272
	125	126	137	93
	138	865	61	120

*Values are normalized to a corresponding value of 100 in the pre-challenge curves.

PI = Guy's Perfusion Index; TP = time-to-peak activity; AI = accumulation index; EI = excretion index.

RESULTS

The networks trained in the number of epochs which are shown in Table 2. A limit of 20,000 epochs was imposed if the network could not converge. This occurred twice in the category which excluded excretion index as an input parameter and 12 times in the category that excluded Guy's Perfusion Index. For the various parameter inclusion patterns: Tables 3A,B show

TABLE 2
Number of Epochs Required to Train the Network for the Various Categories of Input Parameters

Category	Epochs
All	830–2490
No AI	1000–3150
No TP	1710–4710
No EI	4070–20,000
No PI	1870–20,000

See Table 1 for abbreviations.

TABLE 3
Categories of Input Parameters with Corresponding Values of Areas Under the ROC Curves, s.e., z-Score, Significance and Accuracy*

	True-positive and true-negative data only				
Category	ROC area	s.e.	z-Score	Signficance	Accuracy (%)
All	0.946	0.024	-	-	95
No AI	0.942	0.027	0.12	ns	86
No TP	0.838	0.079	1.31	ns	82
No EI	0.679	0.121	2.17	$0.01 < p < 0.05$	64
No PI	0.508	0.121	3.53	$p < 0.001$	55
	All data				
Category	ROC area	s.e.	z-Score	Signficance	Accuracy (%)
All	0.780	0.106	-	-	77
No AI	0.765	0.109	0.10	ns	71
No TP	0.705	0.108	0.50	ns	68
No EI	0.545	0.113	1.52	ns	55
No PI	0.506	0.104	1.84	$p < 0.1$	52

*Significance is the level of the z score for a two-tailed test comparing this category's ROC to that of the "All" category ROC. ns indicates not significant at the 0.1 level.
See Table 1 for abbreviations.

the areas under the ROC curves, s.e. values, z score of each parameter exclusion category against the four input parameter category and its statistical significance. Also shown is the accuracy.

For the true-positive and true-negative data only, the accuracy of the networks varied from 95% to 55% and the area under the ROC curve from 0.946 to 0.508 (Table 3A). The ROC curves of both the excretion index and the Guy's Perfusion Index exclusion categories were significantly poorer than the four input parameter category, shown by the significance levels in Table 3A. The accumulation index and time-to-peak activity exclusion categories were not.

For the complete data set the accuracy of the networks varied from 77% to 52% and the area under the ROC curve from 0.780 to 0.506 (Table 3B). The Guy's Perfusion Index exclusion category was significantly poorer than the four input parameter category at the 0.1 level, the other parameter exclusion categories were not.

DISCUSSION

When the four input parameter trained network was tested on the true-positive and true-egative data only, it was nearly as accurate as that achieved by using conventional algorithmic criteria, giving an accuracy of 95%. When this network was tested on all of the data, it performed better than using the conventional algorithmic criteria, achieving an accuracy of 77% compared to 71%, replacing three false-negative results with one new false-negative. This demonstrates one of the main advantages of the artificial neural network in that it can extract its own best pattern and may provide more information than conventional techniques.

Evaluation of the input parameter exclusion results revealed that accumulation index or time-to-peak activity could be removed without significantly reducing the accuracy of the network. When, however, excretion index was removed the performance of the network deteriorated, not significantly in the complete data set but significantly in the true postive and true negative only data. When the Guy's Perfusion Index was removed the performance of the network deteriorated significantly in both of these categrories.

The CRT technique has previously been shown to be a good excluder of functional RAS in that negative results, based on the evaluation of the renogram curve, can be relied on to exclude this cause of hypertension (*6,9*). The test, however, has been associated with a high level of false positive results (*2,3,6–9*). In a previous work (*13*) we introduced an additional criterion of requiring a positive test to include a decrease in the Guy's Perfusion Index from pre- to post-challenge studies which improved the specificity. The results shown here, using the impartial interpretation technique of artificial neural networks, shows that accurate analysis required the Guy's Perfusion Index and to a lesser extent the excretion index, whereas both the accumulation index and time-to-peak activity could be excluded without significantly affecting the accuracy. Thus, of the four input parameters, the Guy's Perfusion Index and time-to-peak activity were shown to be the most important to the network for accurate interpretation. It may be, however, that other parameters presently in use or the raw curves themselves may be better as input into the artificial neural networks and the analysis could easily be extended to assess these.

CONCLUSION

In this study, the artificial neural network analysis has been shown to be an accurate interpreter of CRT data, surpassing the conventional algorithmic approach by 77% to 71% (ns, $p > 0.5$). It has also been shown to give an insight into the parameters most important for accurate interpretation. Although only four such parameters were used in this study, the analysis could easily be extended to accommodate the many parameters used for interpretation in various institutes.

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Baseline and Postcaptopril Renal Blood Flow Measurements in Hypertensives Suspected of Renal Artery Stenosis

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Renal blood flow (RBF) measurements using first-pass radionuclide angiography with DTPA, a glomerularly filtered agent, failed to show significant differences between normal and stenotic kidneys. Since MAG3 is an ideal agent for the study of RBF, this agent might be an attractive alternative tracer to detect differences in RBF. **Methods:** An angiographically controlled prospective study was performed in 48 hypertensive patients, in whom a diagnosis of renovascular hypertension was suspected on clinical grounds. The study was done to determine whether RBF measurements using first-pass radionuclide angiography with ^{99m}Tc-MAG3 could be helpful in the diagnostic work-up of the patients. Additionally, the study was done before and after ACE-inhibition. **Results:** On renal angiography, 29 patients showed to have normal renal arteries (50 patients had normal kidneys and 8 patients had small kidneys). Nineteen patients had renal artery stenosis (13 uni- and 6 bilateral disease). In the patients with normal kidneys, the mean value of RBF measurements ranged from 10.5% to 10.9% of cardiac output. Only small stenotic and small kidneys with normal renal arteries showed a significant reduced baseline RBF as compared with normal kidneys (both $p < 0.05$); this difference disappeared after ACE-inhibition only for the small kidneys with normal renal arteries. In patients with stenosed kidneys, RBF tended to be reduced both at baseline and after captopril, but the differences with normal kidneys were not statistically significant. After ACE-inhibition RBF increased in the majority of kidneys, but postcaptopril RBF data did not differ significantly from those at baseline. **Conclusion:** RBF measurements using first-pass radionuclide angiography with ^{99m}Tc-MAG3, either before or after ACE-inhibition, cannot reliably discriminate between patients with essential hypertension and patients with renal artery stenosis.

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In 1987, Peters et al. (*1*) described a technique for noninvasive measurements of organ blood flow, which was based on the fractional distribution of cardiac output (CO). When applied to the renal circulation, this method yielded values of renal blood flow (RBF) that were similar to accepted normal values (10%–15% of CO per kidney). Using ^{99m}Tc-DTPA as a tracer, investigators estimated RBF in normal subjects to be 10.4% ± 1.2% of CO for the left kidney and 9.0% ± 1.1% of CO for the right kidney. There was a consistent difference of about 1.5% of the CO at the expense of the right kidney, a phenomenon which was attributed to interference with uptake of tracer by the spleen (*1*).

Patients with both essential hypertension and renal artery stenosis (RAS), the RBF may be reduced, although in the latter category of patients, no correlation between the reduction in flow and the angiographic grading of the stenosis is apparent (*2*). In RAS, however, the RBF is usually reduced only on the affected side. Thus, a further decrease may occur after ACE inhibition (*3*). Therefore, the measurement of individual kidney flows may reveal whether a renal artery stenosis is present or not.

Although Peters et al. performed their studies with DTPA, which is excreted by glomerular filtration, MAG3 may be a good alternative tracer. MAG3 is excreted by both glomerular filtration and tubular excretion (*4*) with renal clearance characteristics comparable to those of ortho-iodohippurate, an agent frequently used for the study of RBF (*5*). If studies could be done with MAG3, the theoretical possibility emerges to combine Peters' method with a quantitative estimation of RBF.

Thus, the present study was designed to evaluate prospectively whether in hypertensive patients, in whom a diagnosis of renovascular hypertension is suspected, measurements of RBF from first-pass radionuclide angiography, at baseline and 2 hr after ACE-inhibition, are able to detect RAS.

MATERIALS AND METHODS

Forty-eight consecutive patients in whom a diagnosis of renovascular hypertension was suspected clinically and antihypertensive medication had been discontinued for at least 2 wk were included in this study (*6*). All patients had ^{99m}Tc-MAG3 measurements of RBF by first-pass radionuclide angiography (*1*) performed on two separate days. On one of these days, baseline data were obtained randomly. On the other day, RBF was determined 2 hr after the patients were administered an oral dose of 25 mg captopril. Before RBF measurements, all patients were given 300 ml of fluid to guarantee urine output of at least 1 ml/min. Patients remained supine during all investigations.

A bolus volume of about 1 ml saline solution containing 148 MBq ^{99m}Tc-MAG3 was given followed by rapid flushing with

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