

Stroke

American Stroke
AssociationSM

A Division of American
Heart Association



JOURNAL OF THE AMERICAN HEART ASSOCIATION

Holter monitoring in patients with transient and focal ischemic attacks of the brain

PJ Koudstaal, J van Gijn, AP Klootwijk, FG van der Meche and LJ Kappelle

Stroke 1986;17:192-195

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 1986 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online ISSN:
1524-4628

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://stroke.ahajournals.org>

Subscriptions: Information about subscribing to *Stroke* is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

25. Fry DL: Acute vascular endothelial changes associated with increased blood velocity gradients. *Circ Res* 22: 165-197, 1968
26. Spence JD: Effects of antihypertensive drugs on blood velocity: implications for prevention of cerebral vascular disease. *Can J Neurol Sci* 4: 93-97, 1977
27. Kikuchi Y, Yamamoto H, Nakamura M: Cerebral atherosclerosis in Japanese. 3. Predilection site of atherosclerotic lesions. *Stroke* 4: 768-772, 1973
28. Osuntokun: Stroke in the Africans. *Afr J Med Sci* 6: 39-53, 1977
29. Harrison MJG, Marshall J: The results of carotid angiography in cerebral infarction in normotensive and hypertensive subjects. *J Neurol Sci* 24: 243-250, 1975
30. Prineas J, Marshall J: Hypertension and cerebral infarction. *Br Med J* 1: 14-17, 1966

Appendix

Special Project Ischemic Brain Disease OD2

Participant Units

Project Coordinator: C. Fieschi
III Clinica Neurologica-Roma

Clinical Units:

C. Argentino, M. Rasura, M. Prencipe, C. Fieschi: Clinica Neurologica dell'Università di Roma. L. De Zanche, A. Saia, G. Meneghetti, S. Manzoni, P. Tonin: Clinica Neurologica dell'Università di Padova. M. Nardini, A. Martini, G. Bonelli, S. Passero, M. D'Ettore: Clinica Neurologica dell'Università di Siena. G. L. Brambilla, R. Rodriguez, Y. Baena, G. Sanguovanni, P. Paoletti: Clinica Neurochirurgica dell'Università di Pavia. D. Inzitari, G. Pracucci, R. Capparelli, R. Taiuti, L. Amaducci: Clinica Neurologica dell'Università di Firenze. F. Tomassello, V. Albanese, A. Scuotto, P. Conforti: Clinica Neurochirurgica dell'Università di Napoli. L. Candelise, P. Perrone, G. Landi, M. Bracchi: Clinica Neurologica dell'Università di Milano.

Biostatistic Unit:

F. Mariani, D. Bardelli, F. Bianchi, R. Cristofani, M. Protti: Istituto di Fisiologia Clinica del C.N.R., Pisa.

Consultant Neuroradiologists:

L. Bozzao (Roma), F. Galligioni (Padova).

Consultant Neuropsychologist:

P. Nichelli (Modena).

Holter Monitoring in Patients With Transient and Focal Ischemic Attacks of the Brain

P.J. KOUDSTAAL, M.D.,* J. VAN GIJN, M.D.,† A.P.J. KLOOTWIJK, M.D.,*
F.G.A. VAN DER MECHE, M.D.,* AND L.J. KAPPELLE, M.D.†

SUMMARY The results of Holter monitoring in 100 patients with transient and focal cerebral ischemia were studied retrospectively. Atrial fibrillation (AF) was found in five patients compared with two from a group of 100 age and sex-matched control patients. Four of these had a previous history of AF or showed AF on the standard electrocardiogram. Episodic forms of sick sinus syndrome, which have also been related to cerebral embolism, were found in 32 of the TIA patients against 13 of the controls ($p < 0.0025$). Sick sinus syndrome was of the bradyarrhythmia-tachyarrhythmia type in 14 of the TIA patients and in three of the controls ($p < 0.01$). The relationship between TIAs and transient sinus node dysfunction could not be explained by concomitant heart disease. It is not yet clear whether the relationship is causal or indirect.

Stroke Vol 17, No 2, 1986

CARDIAC DYSRHYTHMIAS may cause transient neurological symptoms in two ways: (1) by diminishing cardiac output, which may lead to generalized cerebral symptoms, such as dizziness, syncope, etc., and (2) by predisposing to thrombus formation in the heart, with subsequent embolism and focal cerebral dysfunction. The importance of continuous ECG recording in patients with hemodynamically significant dysrhythmias is well established.¹⁻³ In contrast, the value of this technique is uncertain in the detection of dysrhythmias that are associated with emboli, such as atrial fibrillation (AF)⁴ and sinoatrial disease (sick sinus syndrome).^{5,6} Come et al⁷ found that these dysrhythmias occurred only in patients in whom this was previously known from the history or from the electrocardiogram

on admission.⁷ On the other hand, Abdon et al⁸ stressed that Holter monitoring might be important for the detection of mild and episodic sick sinus syndrome, as this may also be related to cerebral embolism.⁹ They found that these transient dysrhythmias occurred significantly more frequently in patients with TIAs and unexplained stroke than in a reference population.⁸ However, this control group was not matched for age and sex.

The present study undertook a retrospective review of Holter monitoring in 100 patients with transient focal cerebral ischemic attacks, and compared the results with those in an age and sex-matched control population.

Patients and Methods

TIA and Control Population

In the period between January 1980 and May 1983, 172 consecutive patients were admitted to the neurological department of the University Hospital of Rotterdam with a diagnosis of transient and focal attacks of cerebral ischemia, lasting less than 24 hours and

From the Departments of Neurology and Cardiology (APJK), University Hospital Dijkzigt, Rotterdam, The Netherlands;* and the Department of Neurology, University Hospital Utrecht, The Netherlands.†

Address correspondence to: Dr. P.J. Koudstaal, Department of Neurology, Dijkzigt Hospital, 40 Dr. Molewaterplein, 3015 GD Rotterdam, The Netherlands.

Received January 5, 1984; revision #2 accepted August 29, 1985.

leaving no deficit. Diagnosis was based upon internationally accepted criteria.¹⁰ The patients were independently interviewed by two physicians, who then discussed the history.¹¹ If they did not agree on the diagnosis, at least one more neurologist was consulted.

In 58 cases, Holter monitoring was not performed. The reasons were technical problems (7 cases), evidence of atrial fibrillation on the initial electrocardiogram (6 cases) and unknown reasons (45 cases), occurring mainly in the period before September 1980 when Holter monitoring was not yet used as a routine investigation in our department. In 14 other patients the period between the neurological symptoms and Holter monitoring exceeded three months, the limit we adopted in this study.

The remaining 100 patients, 74 men and 26 women, ranging in age from 22 to 80 years, with a mean age of 60.9 years, formed the basis of this study. The mean time between recording and neurological symptoms was 15.2 days.

From April 1984 till February 1985, 100 age and sex-matched control patients were selected. These were all in-patients of the University hospitals of Rotterdam and Utrecht and had no previous or present history of focal ischemic brain disease, whether transient or permanent, of peripheral embolism or of treated arrhythmias. Patients who showed physical signs of valvular heart disease or congestive heart failure, and also patients with evidence of recent myocardial infarction on a standard electrocardiogram were excluded. General risk factors for cardiovascular disease such as diabetes mellitus and hypertension were no reason for exclusion. An old (at least one year) myocardial infarction and an enlarged heart on X-ray as a single finding (see table 1) were also accepted.

Ninety-two patients were admitted with neurological disorders not associated with cerebrovascular disease, such as polyneuropathy, spondylotic myelopathy, cerebral tumor, Parkinson's disease, lumbar disk disease or multiple sclerosis. None of the patients had neuromuscular disease known to cause cardiomyopathies. The other eight patients were admitted with urological disorders such as nephrolithiasis and prostate or bladder carcinoma.

Holter Monitoring

All patients were monitored for 24 hours with portable OXFORD MEDILOG 1 tape recorders. All tapes were analyzed semiautomatically at the department of cardiology in Rotterdam. All dysrhythmias that were observed in the recordings of both TIA and control patients were printed out on standard ECG paper, and submitted for a blind review to a cardiologist (APJK).

Classification of Dysrhythmias

All tape reports were reviewed for dysrhythmias which are definitely related to cerebral embolism, such as atrial fibrillation or atrial flutter. As the sick sinus syndrome is possibly related to embolism, the tapes were also reviewed for this disorder, which was defined according to Abdon et al⁸ as the presence of one

of the following: (1) combined sinus bradycardia and sinus arrhythmia with a difference in consecutive cycles of 20% or more and ≤ 50 beats per minute (bpm), or (2) regular sinus bradycardia of ≤ 45 bpm when awake, or (3) sinoatrial block, or (4) sinus arrests of ≥ 1.5 seconds, all irrespective of drug effects. A combination of the sick sinus syndrome and supraventricular tachycardias (heart rate ≥ 100 bpm), specified as atrial tachycardia if P' waves were visible, was classified as the bradyarrhythmia-tachyarrhythmia syndrome. Premature atrial complexes, designated as sporadic if occurring < 20 /hour and frequent if > 20 /hour, were also screened. These complexes are not directly related to embolism, but may be harbingers of atrial fibrillation.

Results

The prevalence of all dysrhythmias has been summarized in table 2. Five TIA patients showed atrial fibrillation, but four of these had already shown AF on a standard ECG.

Of all dysrhythmias, only the episodic sick sinus syndrome occurred significantly more frequently in the TIA patients than in the control population ($p < 0.0025$). Sick sinus syndrome was of the bradytachyarrhythmia type in 14 TIA patients and in three controls ($p < 0.01$).

Of the 32 TIA patients with episodic sick sinus syndrome nine used drugs known to provoke sinus bradycardia (digitalis 6, beta-adrenergic blocking drugs 3) against three of the 13 control patients, or a similar proportion (these three all used beta-blockers).

The mean age of patients with the sick sinus syndrome in both the TIA and the control population was $62 \pm \text{SD } 8.8$ years against 60 ± 11.1 of the other patients ($0.05 < p < 0.10$).

In all patients with multiple ischemic attacks, only one vascular territory was involved. The mean number of attacks in patients with sick sinus syndrome was five, against two in the others ($0.05 < p < 0.10$).

The presence of clinical evidence of cardiovascular disease among TIA patients with and without the sick sinus syndrome is presented in table 3. None of the

TABLE 1 Prevalence of Heart Disease Among TIA and Control Patients

| | TIA patients (n = 100) | Control patients (n = 100) | p |
|---|---------------------------|-------------------------------|---------|
| Previous myocardial infarction | 23 | 3 | <0.0005 |
| Angina pectoris | 18 | 5 | <0.01 |
| History of arrhythmias | 5 | 1 | NS |
| Coronary bypass surgery | 3 | 1 | NS |
| Enlarged heart on x-ray (heart/thorax ratio $> 1/2$) | 12 | 1 | <0.005 |
| Previous ECG with atrial dysrhythmia | 7 | 2 | NS |
| Total number of patients with heart disease | 41 | 8 | <0.0001 |

p values by chi-square test.

TABLE 2 Prevalence of Dysrhythmias Among TIA and Control Patients (for classification of dysrhythmias, see text)

| Dysrhythmia | TIA patients (n = 100) | Control patients (n = 100) | p |
|----------------------------------|---------------------------|-------------------------------|---------|
| Definitely related to embolism | | | |
| Atrial fibrillation or flutter | 5 | 2 | NS |
| Possibly related to embolism | | | |
| Episodic sick sinus syndrome | 32 | 13 | <0.0025 |
| Bradycardia alone | 18 | 10 | NS |
| Bradytachycardia | 14 | 3 | <0.01 |
| Not directly related to embolism | | | |
| Premature atrial contractions | | | |
| Sporadic | 76 | 74 | NS |
| Frequent | 15 | 9 | |
| Supraventricular tachycardia | | | |
| 3-10 cycles | 27 | 25 | NS |
| >10 cycles | 2 | 2 | |
| Atrial tachycardia | | | |
| 3-10 cycles | 4 | 4 | NS |
| >10 cycles | 3 | 2 | |

p values by chi-square test.

individual factors indicating cardiovascular disease were significantly more common among patients with sinus node dysfunction. Cardiovascular disease of any kind was more common among patients with sick sinus syndrome (50% against 36.8%) but the difference did not reach statistical significance ($X^2 = 1.57$; $p > 0.10$).

Because heart disease was relatively rare in the control group (table 1), we investigated whether this might still explain the excess of sick sinus syndrome in TIA patients. Table 4 shows that the difference in sinus node disease is significant only in the patients without obvious heart disease.

Carotid angiography was performed in 35 patients with TIAs. An atheromatous lesion corresponding to the neurological symptoms was found in seven of the twelve patients with sick sinus syndrome and 14 of the 23 without it. A normal angiogram was found in three and six patients, respectively (differences not significant).

Discussion

In this study of 100 patients with transient focal ischemic attacks Holter monitoring showed atrial fibrillation in five patients, against two from a group of 100 age and sex-matched control patients. In four of the five TIA patients AF was previously known from the history or standard ECG. In this respect the diagnostic gain is small, in accordance with the findings of Come et al.⁷

However, mild and episodic forms of sick sinus syndrome, which might also be related to cerebral embolization,⁹ were found in 32 of the TIA patients against 13 in the control group ($p < 0.0025$). The bradyarrhythmia-tachycardia syndrome was

TABLE 3 Prevalence of Clinical Evidence of Cardiovascular Disease Among TIA Patients with and Without Sick Sinus Syndrome

| | Sick sinus syndrome | | p |
|---|---------------------|--------------------|----|
| | Present (n = 32) | Absent (n = 68) | |
| Previous myocardial infarction | 8 | 15 | NS |
| Angina pectoris | 7 | 11 | NS |
| History of arrhythmias | 3 | 2 | NS |
| Coronary bypass surgery | 1 | 2 | NS |
| Cardiac enlargement on x-ray (heart/thorax ratio $> 1/2$) | 4 | 8 | NS |
| Previous ECG with atrial dysrhythmia | 5 | 2 | NS |
| Abnormal finding on echocardiography | 7 (25)* | 12 (47)* | NS |
| left atrial enlargement (> 40 mm) | 3 | 8 | |
| aortic or mitral sclerosis | 3 | 3 | |
| aortic or mitral incompetence | 2 | 0 | |
| left ventricular hypokinesia | 1 | 1 | |
| thrombus/vegetations | 0 | 0 | |
| Total number of patients with heart disease | 16 | 25 | NS |

*In parentheses: number of patients in whom echocardiography was performed.

p values by Fisher exact probability test except for totals which were compared by chi-square test.

found in 14 of the TIA patients against three of the controls ($p < 0.01$).

The diagnosis of sick sinus syndrome was based on the criteria of Abdon et al.,⁸ which may seem more lenient than generally applied.^{5,6} In a long-term follow-up study of 254 patients with episodic sick sinus syndrome, however, the annual risk of a cerebral embolic event was 9.7 per cent for patients with the bradycardia syndrome and 5.3 per cent for patients with bradyarrhythmias alone.⁹ The risk appeared not to be related to the severity of the bradycardia. Yet the mechanism for the occurrence of cerebral embolism in patients with only mild sinus node dysfunction is not clear. One explanation might be that since an important day-to-day variability in dysrhythmias has been reported,¹² patients with only mild sinus node dysfunction

TABLE 4 The Relation Between Heart Disease as a Risk Factor for Dysrhythmias and the Prevalence of Sick Sinus Syndrome Among TIA and Control Patients

| | Sick sinus syndrome | | p |
|---------------------------|---------------------|--------|--------|
| | Present | Absent | |
| Cardiac disease present | | | |
| TIA patients (n = 41) | 16 | 25 | NS* |
| Control patients (n = 8) | 4 | 4 | |
| Cardiac disease absent | | | |
| TIA patients (n = 59) | 16 | 43 | <0.01† |
| Control patients (n = 92) | 9 | 83 | |

p values by Fisher exact probability test* and chi-square test.†

tion in one recording might show more severe forms on another occasion. It would be interesting if in future studies of this nature, patients had more than one 24-hour ambulatory recording.

Not all cases of sick sinus syndrome necessarily represent intrinsic atrial disease. First, sinus node dysfunction may also be provoked by certain drugs, such as digitalis and beta-blockers. Nine of the TIA patients and three of the controls with sick sinus syndrome were on one or both of these drugs at the time of Holter monitoring. Even if these cases were omitted, the difference between the two groups would still be significant ($X^2 = 6.13$; $p < 0.02$). Moreover, Abdon et al reported that patients with drug-induced sick sinus syndrome had the same rate of embolism as spontaneous forms.⁹ Second, sinus bradycardia may occur in metabolic disorders such as hypothyroidism and hypothermia,¹³ but none of these was present in the two populations. Finally, cardiac dysrhythmias may be the result rather than the cause of brain damage.¹⁴ However, stroke patients are far more likely to show these secondary dysrhythmias than TIA patients, and these were intentionally excluded from the study.

Half of the patients with sick sinus syndrome in this study did not show clinical evidence of cardiac disease. Furthermore, the prevalence of cardiovascular disorders among patients with and without sinus node dysfunction was not statistically different, which is in accordance with an earlier study.⁸ From the few post-mortem studies in patients with sinoatrial disease, it appears that ischemic heart disease may account for some cases, but in the majority of patients the cause remains unknown.¹⁵ In the patients from this study it would have been impossible to anticipate from the presence of clinical evidence of cardiovascular disease whether Holter monitoring would be rewarding. This means that many occult forms of sick sinus syndrome can be effectively identified only by means of long-term ECG monitoring. The yield might have been even larger if we had been able to monitor patients longer than 24 hours.

One might argue that the preponderance of sinus node dysfunction in the TIA patients merely reflects the lower prevalence of cardiovascular disease in the control group. However, we found that the difference in sick sinus syndrome between the two groups was significant only in patients without overt heart disease. Although it is impossible to exclude a similar relationship with heart disease, because of the small number of such patients in the control group, this finding makes it unlikely that the different prevalence of heart disease among TIA and control patients accounts for the observed difference in sinus node dysfunction. Another possible objection might be that the control patients were investigated a few years later than the TIA patients. Drug use, however, was not responsible. Furthermore, all tapes were analyzed by the same person and all recordings were blindly reviewed by one cardiologist.

In conclusion, we found an association between transient sinus node dysfunction and TIAs. The pro-

portion of sick sinus syndrome in the TIA patients (32%) is similar to the findings of Abdon et al.⁸ It is not clear whether the relationship is causal or indirect. A common factor such as atherosclerosis might induce both TIAs and sinus node dysfunction, although the relationship was not found in patients with ischemic heart disease. Unlike Abdon et al. we could not find other indices of a cardiac source of emboli in patients with sinoatrial disease, such as an excess of normal carotid angiograms or multiple foci of the TIAs. On the other hand, preliminary data indicate that these transient dysrhythmias predispose to cerebral embolization.⁹ Prospective studies are necessary to unravel the association between sinus node disease and TIAs. If a causal relationship is confirmed, then clinical trials of therapeutic measures such as pacemaker implantation, withdrawal of responsive drugs and/or antiarrhythmic drug treatment in the prevention of stroke in TIA patients with sinus node disease are justified.

Acknowledgment

The authors wish to thank Prof. Dr. A. Staal and Dr. M. Vermeulen for valuable comment, Miss Angela Peterse of the Cardiolab Rotterdam for analyzing the tapes, Drs. H.J.A. Schouten for statistical advice and Mrs. J. Doornbosch-Konijn and Mrs. B. Mast-van der Woude for secretarial help.

References

- Jonas S, Klein I, Dimant J: Importance of Holter monitoring in patients with periodic cerebral symptoms. *Ann Neurol* 1: 470-474, 1977
- Francis DA, Heron JR, Clarke M: Ambulatory electrocardiographic monitoring in patients with transient focal cerebral ischemia. *JNNP* 47: 256-259, 1984
- McAllen PM, Marshall J: Cardiac dysrhythmia and transient cerebral ischemic attacks. *Lancet* 1: 1212-1215, 1973
- Wolf PA, Dawber TR, Emerson Thomas H, Kannel WB: Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 28: 973-977, 1978
- Rubinstein JJ, Schulman CL, Yurchak PM, De Sanctis RW: Clinical spectrum of the sick sinus syndrome. *Circulation* 46: 5-11, 1972
- Fairfax AJ, Lambert CD, Leatham A: Systemic embolism in chronic sinoatrial disorder. *N Engl J Med* 295: 190-192, 1976
- Come PC, Riley MF, Bivas NK: Roles of echocardiography and arrhythmia monitoring in the evaluation of patients with suspected systemic embolism. *Ann Neurol* 13: 527-531, 1983
- Abdon NJ, Zettervall O, Carlson J et al: Is occult atrial disorder a frequent cause of non-hemorrhagic stroke? Long-term ECG in 86 patients. *Stroke* 13: 832-837, 1982
- Abdon NJ, Jönsson BM: High risk of systemic embolization in episodic sick sinus syndrome. In: Meere C (ed): Proceedings of the Vth world symposium on cardiac pacing. Montreal Pace Symposium, chapters 17-11, 1979 (Abstract: *PACE* 2: A50, 1979)
- The Ad Hoc Committee on the classification and outline of cerebrovascular disease. II. (Chairman Millikan C). *Stroke* 6: 566-616, 1975
- Kraaijeveld CL, van Gijn J, Schouten HJA, Staal A: Interobserver agreement for the diagnosis of transient ischemic attacks. *Stroke* 15: 723-725, 1984
- Winkle RA: Detection of patients at high risk for sudden death; the role of electrocardiographic monitoring. In: Kulburtus HE, Wellens HJG (eds): Sudden death, developments in cardiovascular medicine. Martinus Nijhoff publishers b.v., pp 275-296
- Rosen KM, Swiryn SS: Bradyarrhythmia-sinus node dysfunction and conduction defects. In: Petersdorf RG et al (eds): Harrison's principles of internal medicine, 10th ed: 1364-1372, 1983
- Norris JW, Frogatt GM, Hachinski VC: Cardiac arrhythmias in acute stroke. *Stroke* 9: 392-396, 1978
- Fairfax AJ, Lambert CD: Neurological aspects of sinoatrial heart block. *JNNP* 39: 576-580, 1976