Embolic Complications in Paroxysmal Atrial Fibrillation

PALLE PETERSEN, M.D., AND JOHN GODTFREDSEN, M.D., PH.D.

SUMMARY The incidence of embolic complications among 426 patients with initial paroxysmal atrial fibrillation (PAF) was analysed. A distinct clustering of emboli was seen at the time of onset of PAF. After transition to chronic atrial fibrillation (CAF), which developed in 141 patients (33.1%), the incidence of emboli was seen to rise to a new level several times higher than the incidence level for patients with PAF. Also in this group a distinct clustering of emboli was seen during the first year after transition to CAF.

On this background it is suggested that patients with PAF may benefit from treatment with anti-arrhythmic agents in order to prevent the development of CAF and that anticoagulants for stroke prevention seems especially desirable in atrial fibrillation (AF) of recent onset.

AF is found in 0.4% of the adult population.1 - 2 The prevalence increases with age, being 2-4% after 60 years of age.3 - 5 A well-known and often serious complication in AF is arterial thromboembolism, occurring with an overall rate of 25%.4 - 7 with the highest frequency at the time of onset of AF.4 - 8 9

The only available study of the risk of embolic complications in PAF showed a rate of cerebral emboli of 6.4% during a 10-year period,10 but further details on etiological differences, and the duration of PAF as related to embolism are unknown.11

Because it is of great clinical importance to know whether PAF carries the same risk of embolic complications as CAF, the purpose of this retrospective study was to relate the rate of systemic embolic complications to the underlying etiology, to the number of AF paroxysms, to the type of AF (paroxysmal or chronic), and to the time of onset of the initial AF episode.

Methods

The study group consisted of 426 consecutive hospitalized patients with PAF (males: 213, females: 213, median age: 66 years — range 20-89 years). The study was retrospective and comprises all cases with PAF admitted to a major Danish county hospital in the period 1940-1967. Some data on these patients was published in 1975,8 but due to the recent and renewed attention to AF as a major cause of stroke8,9 the present study is a re-evaluation of the original material. Every case had the initial episode of AF verified by ECG, and a documented conversion to sinus rhythm either spontaneously or after treatment during admission to the hospital. The underlying heart diseases are shown in table 1. The follow-up consisted of a thorough scrutiny of all medical charts and records for every patient including death certificates. Three years after closing the entry into the study all survivors (95 patients) were reexamined for a history of embolic complications and cardiac status was assessed including an ECG.

The criteria for systemic arterial embolism were clinical signs or a medically confirmed history (or death certificate) of an acute onset of ischemia, in the cerebral arteries, in the visceral arteries or in the peripheral arteries. Since it is impossible to distinguish thrombotic from embolic stroke,4 all strokes occurring in patients with AF were recorded without respect to probable stroke mechanisms. Cases not witnessed by the attending physician or confirmed by a subsequent hospital admission were not accepted nor were cases of transitory cerebral ischemia or retinal ischemia.

No patients were treated with anticoagulants because of AF, whereas patients with an established embolic complication received coumarin drugs if not contraindicated.

As endpoints were recorded the time of death or the final examination in the survivors. Also recorded were: 1) Time from the initial onset of AF to an embolic episode (TTE), and 2) Time from the initial AF onset to transition to CAF as documented by serial ECG's (TTT). All times were recorded in months.

The median duration of the follow-up for the entire series was 3.5 years (range: 0-24 years). In the retrospective analysis of the course two groups of patients emerged: A: 285 patients with initial PAF, one or more recurrent paroxysms of AF, but without transition to CAF (i.e. persisting PAF). The median follow-up in this group was 2.9 years (range: 0-16.2 years). B: 141 patients with initial PAF, one or more relapses, and sooner or later transition to CAF (i.e. PAF with transition). The median follow-up in this group was 9.0 years (range: 0-24 years), due to a lower median age at AF onset as compared to group A (63 years vs. 68 years, p < 0.001). Accordingly, at the termination of the study 229 patients (80.4%) and 102 patients (72.3%) in group A and B respectively were dead. The cause of death was in every case confirmed by a check of the death certificates and a cross-check with the records of the patients family physician.

The total number of embolic complications in the two groups was calculated, but with attention to the follow-up time and to the fact that some patients in group B developed emboli during the course of PAF and some during CAF, the basis of the statistical analysis was a classification of the patients into 4 groups,
namely PAF-patients with and without embolic complications and CAF-patients with and without emboli. The rate of transition from states without emboli to states with emboli, from PAF to CAF and the risk of death was analyzed using Cox’s regression model for failure time data with sex, age and etiology as explanatory variables. In connection with the analysis of rates of transition to states with embolic complications, the occurrence of CAF was included as a possible time-dependent covariable, while the occurrence of emboli was treated as a time-dependent covariate in the analysis of transition to CAF. In the analysis of risk of death both occurrence of emboli and occurrence of CAF were treated as time-dependent variables. Regression parameters were estimated by standard maximum likelihood methods and the importance/significance of the explanatory variables and the time-dependent covariates was evaluated by likelihood ratio tests. Both forward and backward selection strategies including and excluding factors were adhered to.

Results

In 273 patients (64%) of the entire series the initial AF paroxysm subsided within one week, but in 227 patients (53.3%) the duration was no more than 1–2 days. In only 5 patients the duration of the initial PAF episode before spontaneous reversion to sinus rhythm was more than a year. Three patients received electrical conversion but without long-lasting effect and in 65 patients quinidine therapy was tried with long-lasting effect in only 25 patients. Of these patients 34 patients (50%) developed CAF. No episodes of emboli occurred in association with the conversion trials.

Systemic arterial emboli occurred in 79 patients (18.5%) of the entire series (table 1), of which 46

(58.2%) were cerebral. The rate of embolic complications varied significantly with the underlying etiology as 59 patients (15.9%) with non-RHD and 20 patients (35.7%) with RHD had embolic complications ($p < 0.00005$). When calculated in patient groups with one ($n = 287$), 2–5 ($n = 63$) or more than 5 ($n = 76$) paroxysms of AF, there was no statistical difference in the rate of embolism.

Tables 2 to 4 summarise the results of the statistical analyses of transitions and mortality, while table 5 reports the distribution of the patients at given times according to PAF/CAF state, occurrence of embolic complications and survival, censoring or death. Table 6 shows the observed number of transitions between states. Thus tables 5 and 6 are purely descriptive, whereas the result of tables 2 to 4 are based on analyses where time was treated as a continuous variable measured in months as stated above.

Table 2 shows that occurrence of embolic complications depends on PAF/CAF, but not on sex, etiology or age. As the transition from PAF to CAF depends on etiology (RHD), but not on sex or age (table 4), an indirect interaction between etiology and occurrence of embolic complications is implied. Finally, occurrence of CAF is also found to depend on a previous occurrence of embolic complications (table 4), while mortality is only dependent on embolic complications and age (table 3).

Table 6 shows the incidence rate of embolic events the first five years after the initial diagnosis of AF. In persisting PAF the incidence of embolism was 6.8% in the first month, thereafter decreasing to a very low incidence rate, about 2% per year for the following 5 years. In patients with transition to CAF the first year incidence rate was 13.3%, thereafter decreasing to about 4% for the rest of the following 4 years. The yearly mean incidence of emboli during the first five years was 2.0% in patients without transition to CAF and 5.1% in patients after the transition was established. However, in both groups a distinct clustering of
Table 5 Embolic Complications in 426 Patients with PAF

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>With PAF without complications</th>
<th>With PAF with complications</th>
<th>With CAF without complications</th>
<th>With CAF with complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive</td>
<td>Censured*</td>
<td>Dead*</td>
<td>Alive</td>
</tr>
<tr>
<td>Initial state†</td>
<td>344</td>
<td>—</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>After 1 year</td>
<td>252</td>
<td>107</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>219</td>
<td>128</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>178</td>
<td>147</td>
<td>13</td>
<td>13</td>
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<td>4</td>
<td>143</td>
<td>164</td>
<td>7</td>
<td>02</td>
</tr>
<tr>
<td>5</td>
<td>122</td>
<td>167</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>189</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>25‡</td>
<td>—</td>
<td>202</td>
<td>—</td>
<td>5</td>
</tr>
</tbody>
</table>

*Cumulated data.
†With death occurring less than 1 month after PAF.
‡Terminal state after 24 years of follow-up.

Discussion

That CAF carries an increased risk of stroke seems well-established. In the Framingham study,12 dealing only with CAF, an increased risk of stroke was found. AF in absence of RHD was associated with more than a five-fold increase in stroke incidence, while AF with RHD had a 17-fold increase compared to the controls without AF.

In spite of the serious consequences of embolic complications, no clinical studies have solved the problems concerning the rate of embolization in PAF as compared to CAF. Thus, Takahashi et al10 found embolic complications in 8 out of 94 patients with PAF, but from the data it was not possible to determine whether the strokes occurred before or after the PAF became CAF, which occurred sooner or later in 25% of the cases.

It is well-known that the risk of stroke is increased in AF due to RHD as compared with other etiologies,4,5,7,12 and this was confirmed in this study. However in RHD-patients most embolic complications were seen at the time of or after transition to CAF. In this series of RHD 10 patients had mitral incompetence (10/56 = 17.9%), but only one had emboli, thus confirming the clinical impression, that mitral incompetence is rarely complicated by embolism. The two etiologic groups with ischemic/hypertensive heart disease and other heart diseases did not differ significantly in the number of embolic complications (table 1).

In the 141 patients who eventually had CAF 13

Table 6 Transition to CAF and Incidence of Stroke

<table>
<thead>
<tr>
<th>New occurrence of CAF*</th>
<th>Occurrence of embolic complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With PAF†</td>
</tr>
<tr>
<td>Initial state (1 month)</td>
<td>22 (5.2%)</td>
</tr>
<tr>
<td>Remaining of 1 year</td>
<td>22 (2.7%)</td>
</tr>
<tr>
<td>2 years</td>
<td>7 (2.8%)</td>
</tr>
<tr>
<td>3 years</td>
<td>20 (9.1%)</td>
</tr>
<tr>
<td>4 years</td>
<td>13 (7.3%)</td>
</tr>
<tr>
<td>5 years</td>
<td>14 (8.9%)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>25 —</td>
</tr>
<tr>
<td>10-25 years</td>
<td>18 —</td>
</tr>
<tr>
<td>Total</td>
<td>141 —</td>
</tr>
</tbody>
</table>

*Percentages calculated with respect to the number of living PAF-patients at the beginning of the year.
†PAF/CAF — state at the beginning of the period. Percentages calculated with respect to the number of living PAF respective CAF patients without complications at the beginning of the year. In brackets are patients with new occurrence of CAF and embolic complications.
‡Percentages calculated with respect to the total number of PAF and CAF patients without complications at the beginning of the year.
patients had emboli at the time of transition to CAF. This basic retrospective break-down of the series raises an important problem, namely as to whether the 13 cases of embolism belong to the PAF or the CAF group. A careful analysis of the clinical circumstances at the transition from PAF to CAF in these 13 patients showed, that in 9 patients the embolism definitely occurred after CAF was established. In four patients several paroxysms of PAF preceded the embolic episode, which in fact occurred at the same time as the PAF became chronic. Thus, especially in a retrospective study, one can speculate whether these four patients should be classified as PAF or CAF, but as no episodes of sinus rhythm were evidenced after the embolism, we found it reasonable to place them in the CAF group.

Moreover the decremental analysis, based on the retrospective defined time course for the two patient-groups PAF and PAF with transition to CAF, showed highly significant differences in the rate of embolism during all the years studied (table 2), and other reported figures show a difference in embolism between patients with PAF and CAF.

In this study the number of embolic complications is probably underestimated as only medically attended strokes were included. However, in PAF a yearly mean frequency of 2.0% was found. This was about twice the frequency as compared to the frequency in epidemiological series without AF. In the Danish study the average annual incidence of strokes was 0.64% in individuals aged 65–74 years, but the higher frequency obtained in this study may be accounted for by the fact that the patients were selected from a hospital-based material, and that all types of embolic complications were included. Moreover the risk of emboli decreased one year after the onset of AF regardless of whether the fibrillation was chronic or paroxysmal.

Our finding of a mean yearly incidence rate of embolism of 5.1% in CAF is close to the 8% found in a previous clinical study. In contrast to the yearly incidence rate a clustering of embolic complications was seen both at the time of onset of PAF and at the time after transition to CAF (table 6). This is in accordance with the results of the Framingham study, where 37.3% of the strokes were seen during the first year after the initial AF diagnosis with a clustering of stroke events at the onset of AF. Thus in this clinical study, contrary to what might be expected, PAF was associated with a lower incidence of thromboembolic events than CAF.

Somewhat surprisingly the number of AF-attacks was without influence on the risk of embolization, but the reason for this may be inadequate registration of the attacks, as the majority of the patients after the initial hospitalization were followed in the out-patient clinic or by their family physician. Accordingly, the number of AF-attacks in this retrospective study may be underestimated, but this does not change the fact that few embolic complications were seen during the course of PAF. Moreover our finding of very few strokes in PAF compared to CAF can not be explained by the age difference between the groups as the patients in group B were younger than the patients in group A. The high mortality found in both group A and B may be explained firstly by the long follow-up time and secondly by the fact that the study was hospital-based.

As pointed out by others, there is reason to believe that the majority of strokes in AF is on the basis of cerebral embolism, but the reason why PAF carries a low rate of embolic complications compared to CAF is unknown, and future studies will have to show whether other factors such as reduced cerebral blood flow and high blood viscosity, for example during diuretic treatment of heart failure, contributes to the development of strokes in AF. Moreover the effectiveness of coumarin drugs in the prophylaxis of thromboembolic complications in AF is only assumed, not proven, and the importance of these problems must be emphasized.

The results of this study are pertinent, firstly because of the low embolic rate in PAF compared to the rate in CAF, and secondly because of the distinct clustering of embolic events both during the first year after the onset of PAF and immediately around the time of transition to CAF. On this basis future trials of anticoagulants for stroke prevention in AF and particular in recent-onset AF seem desirable. Besides, it is possible that more aggressive prophylactic treatment with antiarrhythmic agents in PAF may postpone the development of CAF and thereby the high risk of embolic complications, but future studies will have to show whether this is true or not.

Acknowledgment

The authors wish to thank the statistician Svend Kreiner, M.Sc., for performing the statistical analyses.

References

12. Wolf PA, Dawber TR, Thomas He Jr, Kannel WB: Epidemiologic
Cerebral Hemorrhagic Infarction at Autopsy: Cardiac Embolic Cause and the Relationship to the Cause of Death

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SUMMARY In 48 patients dying within 15 days following a supra-tentorial cerebral infarct, the presence of hemorrhagic infarction at autopsy was related to a cardiac embolic cause of the infarct, and to the cause of death. Hemorrhagic infarcts were more common among patients dying from brain herniation than among those dying from a non-cerebral cause. Cardiac embolic strokes were more often hemorrhagic at autopsy than strokes without such cause; this could be explained by a significant higher rate of brain herniation and death after embolic stroke. On the other hand infarcts with extended hemorrhages more often tended to have a cardiac than a non-cardiac cause. These data, together with earlier clinical findings suggest that autopsy studies are biased in relating hemorrhagic infarction almost exclusively to a cardiac embolic cause of stroke, although cardiac emboli may produce more extended hemorrhages.

RECENT STUDIES show that early anticoagulation can safely be used in cardiac embolic strokes.14 The timing of such treatment, however, remains controversial.54 Incidental clinical reports on cerebral complications of anticoagulant therapy2311 and autopsy studies support the fear for such complications because a high rate of hemorrhagic infarcts was related to embolic stroke.1214 On CT, however, hemorrhagic infarction is rarely seen1518 even in embolic stroke.124 Furthermore, hemorrhagic infarction is most prevalent in large infarcts with mass effect.19 Embolic strokes relatively often result in large infarcts with bad outcome.142024 Therefore, autopsy findings are probably biased in establishing a high rate of embolic cause in cases with hemorrhagic infarction. The finding of many more embolic strokes in autopsy studies12132025 than in clinical and epidemiological studies222627 also suggest such bias. Alternatively, the incidence of clinical emboli might be underestimated because of the difference between autopsy and clinical criteria for cardioembolic infarction. Moreover, CT might miss minor hemorrhagic infarction. On the other hand a substantial number of patients with clinically diagnosed cardioembolic stroke have concomitant carotid artery disease as a possible cause of their stroke.628 Clinically the number of cardioembolic strokes might well be overestimated. If the presence of hemorrhages in an infarct is primarily a function of the size of the infarct, one ought to find hemorrhagic infarction more often in cases dying from the direct consequence of large infarction which is brain herniation, regardless of the cause of the infarct. Therefore, in a consecutive autopsy series of ischemic stroke, we studied the incidence of hemorrhagic infarction in patients with and without brain herniation.

Methods

Clinical data and autopsy findings of patients who died between 01-01-1979 and 01-01-1985 within 15 days following a supra-tentorial, non-lacunar, focal cerebral ischemia were evaluated. On pathological examination the cerebral infarct compatible with the recent stroke was listed as either ischemic necrosis (IN), or as hemorrhagic infarction (HI) when on macroscopic examination a (partial) hemorrhagic infarct was present and confirmed by microscopic examination.29 The extend of hemorrhage was judged as 'small', if one or some small areas of petechial hemorrhages were present, or as 'large' when areas of confluent hemorrhages were observed. Examples of both categories are represented in figures 1 and 2. The cause of death was judged to be either 'cerebral' when death had resulted directly from brain herniation, or 'non-cerebral' when death had resulted from an other cause such as: pneumonia, myocardial infarction, pulmonary embolus, etc.

Although the study was partially done on retrospect, apart from two cases these data could be gathered without exception since they were systematically mentioned in the pathologist's report. Patient records were reviewed for the following features: patient's age and sex; number of days between stroke and death; cardiac
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Stroke. 1986;17:622-626
doi: 10.1161/01.STR.17.4.622

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