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Cerebrovascular accidents in adult patients with congenital heart disease

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ABSTRACT

Objective To investigate the prevalence and characteristics of cerebrovascular accidents (CVA) in a large population of adults with congenital heart disease (CHD).

Methods and results In a retrospective analysis of aggregated European and Canadian databases a total population of 23 153 patients with CHD was followed up to the age of 16—91 years (mean 36.4 years). Among them, 458 patients (2.0%) had one or more CVA, with an estimated event rate of 0.05% per patient-year. Permanent neurological sequelae were noted in 116 patients (25.3%). The prevalence of CVA in selected diagnostic categories was as follows: open atrial septal defect 93/2351 (4.0%); closed atrial or ventricular septal defect 57/4035 (1.4%); corrected tetralogy of Fallot 52/2196 (2.4%); Eisenmenger physiology 24/467 (5.1%); other cyanotic 50/215 (23.3%); mechanical prostheses (29/882 (3.3%). Associated conditions in patients with CVA were absence of sinus rhythm (25%), transvenous pacemakers (7%), endocarditis (2%), cardiac surgery (11%) and catheter intervention (2%), but with the exception of absent sinus rhythm these were not significantly more prevalent in patients with CVA.

Conclusion CVA are a major contributor to morbidity in this young population despite absence of classical cardiovascular risk factors. Although the prevalence of CVA in patients with CHD appears low, it is 10—100 times higher than expected in control populations of comparable age. Residua occur in a strong minority of patients. The subjects at highest risk are those patients with CHD with cyanotic lesions, in whom the prevalence is over 10-fold above the average.

INTRODUCTION

Cerebrovascular accidents (CVA) may occur as a direct complication of congenital heart disease early in childhood or during later years. Causes of CVA in patients with congenital heart disease (CHD) include emboli from the heart (with or without the presence of atrial arrhythmias) or from the central arteries, paradoxical emboli from the venous bed or haemorrhage. They may be related to the presence of a shunt (paradoxical embolism), to a previous repair (eg, valve procedures or intravascular devices) or to infection. They may occur at the time of a cardiovascular procedure as a result of thromboembolism, air embolism, or hypoperfusion and ischaemia. In patients with erythrocytosis they may be related to rheological problems of hyperviscosity or spherocytosis due to iron deficiency. In addition, acquired cardiovascular risk factors such as smoking, diabetes and hypertension may also contribute to the risk of CVA as the population is ageing. Even though CVA are rare, they often leave sequelae which may add significantly to the disease burden in this relatively young population. There are numerous reports of single cases and case series[1—3] but epidemiological data are lacking. This retrospective multicentre study aims to assess the prevalence of CVA in a large population of adults with congenital heart disease (ACHD) and to identify subgroups of patients at risk and circumstances which may place these patients at special risk.

METHODS

Data were pooled from several designated ACHD databases and analysed retrospectively. Participating centres were the Academic Medical Centre (Concor database, Amsterdam, The Netherlands), Royal Brompton Hospital (London, UK), Toronto Congenital Cardiac Centre for Adults located at the Toronto General Hospital (Toronto, Canada) and University Hospitals at Bern and Basel, Switzerland. Centres were asked in the summer of 2007 to list and specify all patients in whom a CVA was coded in their database or noted in the records. By this approach no uniform definition of CVA was possible. All charts of the patients coded with CVA were reviewed according to a predesigned data abstract sheet which included a patient's date of birth and gender, diagnosis, age at last follow-up, age at first CVA, recurrence of CVA, neurological sequelae, aetiology of CVA, relation to cardiac procedures (CVA occurring with immediate temporal relation to, and presumably caused by, cardiac surgery or catheterisation according to case records), rhythm at the time of CVA, anticoagulation at the time of CVA and cardiovascular risk factors such as diabetes, hypertension, smoking, thrombophilia, use of contraceptive hormones. In addition, each centre provided a description of their total ACHD population followed up at the time, with details of age, gender, follow-up duration and diagnosis.

Inclusion criteria were somewhat different at the various centres. In general, all patients followed up in the adult CHD clinics were included. Patients are usually referred to these clinics by the regional paediatric cardiology centres. However, some patients may be lost to follow-up because they move away from the region or for other reasons. In addition, patients with early deaths are not included in the adult databases. Therefore this clearly is not a consecutive case series. Patients with isolated patent foramen ovale (PFO) were also excluded from the analysis.

RESULTS

The total adult population with CHD comprised 23 153 patients (11 433 male, 11 720 female) with a follow-up of 842 769 patient years. The mean age at last follow-up was 36.4 years (range 16—91 years).

A total of 458 cases with CVA were identified (2.0% of the total adult CHD population followed up). The calculated incidence per year of follow-up was 0.05. Recurrent CVA were noted in 12.0% of cases. Persistent neurological deficits were present in 25.3% of patients. A haemorrhagic origin was noted in 1.5%, there was only one case of warfarin bleeding. An embolic origin was proved in 19.1% and presumed in 72.1% of the cases. Some cases remained unclear from the records. Imaging data (head CT or MRI) were available in only one-third of cases and since they were not recorded uniformly they were not analysed further. Mortality also was not analysed since death due to CVA was exceptionally rare in this series. Other causes of death were not within the scope of this study.

The first CVA occurred at a mean age of 37.0 years, patients ages ranging from 0.5 to 85 years. Therapeutic interventions (first if multiple) had been performed in 389 patients (85%) at a mean age of 22.6 years (range 0—82). Mean age at correction was significantly higher in patients with atrial septal defect (ASD) (48.3 years, range 5—82, p<0.00001). The time course of occurrence of CVA is shown in figure 1. The occurrence of CVA peaked around the age of 30, with more cases occurring at younger ages rather than later in life (figure 1, upper panel).

The prevalence of CVA in various major diagnostic categories is shown in table 1, where the prevalence is given in relation to the number of all patients in the major diagnostic subgroups. A striking 23.3% was noted in non-Eisenmenger cyanotic patients (mostly patients with single ventricle with or without palliation), whereas a prevalence slightly but significantly above
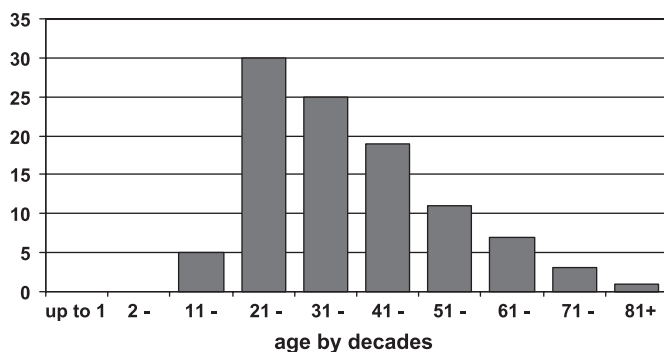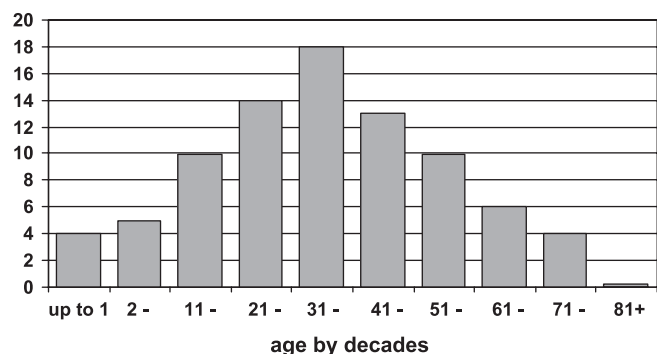
average was seen in patients with Eisenmenger syndrome (5.1%), in patients with an open ASD (4.0%), in Fontan patients (4.1%), complete TGA after an atrial switch procedure (3.2%) and in patients with mostly left-sided mechanical prosthetic valves (3.3%). The same differences are seen in an alternative depiction as shown in figure 2. Risk factors associated with stroke are presented in figure 3, again in CVA cases as compared with the entire study population where appropriate (upper panel). The prevalence of CVA in patients presenting with risk factors is shown in the lower panel. In patients with a CVA the following conditions were observed: absence of sinus rhythm (25.1%), the relation to cardiac surgery (11.1%), and presence of a pacemaker (7.2%). Furthermore, in patients with a CVA contraceptive hormones were involved in 2.6%, endocarditis, coagulopathy or catheter procedures in 2.2% each. Only one stroke was reported to be due to warfarin-associated bleeding. Most of these associated factors were present equally in patients with CVA and in the entire population, with the exception of absent sinus rhythm which was significantly more prevalent in patients with CVA than in the total ACHD population (p<0.001).

DISCUSSION

The incidence of CVA in adult patients with congenital heart disease may seem low when considering the rate of 0.05% per year of follow-up. However, in this population with a relatively young mean age of 36 years at last follow-up, this figure is 10—100 times higher than in an otherwise healthy general population.[4] Our data show that a CVA may occur at any age, the occurrence being normally distributed around a mean age of 37 years (figure 1). The incidence of CVA by age group cannot be analysed meaningfully, since the age distribution of the entire study population is known at the time of follow-up, which was not the time of CVA occurrence since this was not a 'study end point'.

In comparison, the Euro Heart Survey on adult CHD reported a stroke incidence of 4% in over 4000 patients observed over

Figure 1 (Upper panel) Distribution of cerebrovascular accidents in per cent by decades of patients' age. (Lower panel) Distribution of adult congenital heart disease study population in per cent by decades of age at follow-up.

Table 1 Patients with CVA and total ACHD population in various diagnostic categories

|	Total population	CVA cases	p Value (χ^2 test between cases and total population)
Number	23 153	458 (2.0)	
Mean age at follow-up (range)	36.4 (16—91)	45.4 (14—86)	
Mean age at first CVA (range)	—	37.0 (0.5—85)	
Male gender	11 433 (49.4 % of ACHD population)	228 (49.8 % of CVA cases)	NS
Closed ASD/VSD	4035	57 (1.4)	<0.005
Open ASD	2351	93 (4.0)	<0.0001
Fallot's tetralogy	2196	52 (2.4)	NS
TGA atrial switch	690	22 (3.2)	<0.02
Coarctation	2027	41 (2.0)	NS
Fontan	484	20 (4.1)	<0.001
Eisenmenger	467	24 (5.1)	<0.0001
Cyanotic (non-Eisenmenger)	215	50 (23.3)	<0.0001
Mechanical valve prostheses	882	29 (3.3)	<0.005
Miscellaneous	10 688	70 (0.7)	

Results are shown as the percentage of the total population (if not stated otherwise). ACHD, adults with congenital heart disease; ASD, atrial septal defect; CVA, cerebrovascular accident, TGA, transposition of the great arteries; VSD ventricular septal defect.
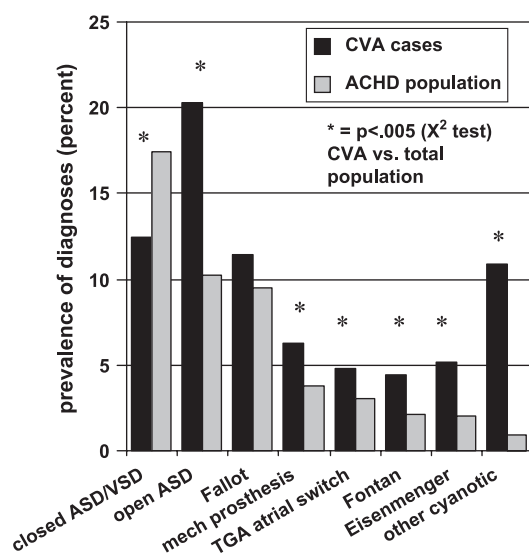
Figure 2 Prevalence of diagnoses in patients with CVA cases as compared with the entire ACHD study population. ACHD, adult congenital heart disease; ASD, atrial septal defect; CVA, cerebrovascular accident, TGA, transposition of the great arteries; VSD ventricular septal defect.

5 years.[2] The higher rate reported from these authors probably reflects a different patient population with a selection bias towards more severe lesions. Indeed the Euro Heart Survey was a cross-sectional study on a highly selected patient cohort. Our own analysis is also likely to be distorted by two facts. First, a number of cases occurring in childhood may have been lost in the databases and second, many of the older patients were included in the databases because a congenital anomaly, in particular an ASD, was detected at the time of a CVA occurring at this age. This may indeed lead to some distortion of reporting. In addition, loss of sinus rhythm and cardiovascular risk factors presumably are more common in the subgroup of patients with closed ASD owing to their advanced age.

The occurrence of a CVA is most marked in cyanotic patients, both in those with the Eisenmenger syndrome and even more so in those without Eisenmenger physiology. One reason for this difference might be that cyanotic patients with non-Eisenmenger physiology supposedly have more atrial arrhythmias as in these patients the anatomy mostly involving the atria is more complex. A very similar stroke rate of 0.3—1.0 % per year of follow-up was reported in the second natural history study of ventricular septal defect for patients with the Eisenmenger syndrome (unoperated and operated, respectively).[5] The stroke rate was also observed to be three times higher in cyanotic patients in the Euro Heart Survey.[2] Most of these patients have single ventricle physiology with important right-to-left shunting, making them vulnerable to systemic emboli. In addition, iron deficiency due to repeated venesection resulting in spherocytosis and hyperviscosity may contribute to ischaemic strokes. Prophylactic anticoagulation may be helpful in such cases, particularly after a first embolic event or when additional risk factors such as atrial fibrillation are present, but this treatment is hampered by several problems in adult patients with cyanotic CHD. Meticulous surveillance and monitoring of international normalised ratio values are often difficult owing to methodical problems related to high haematocrit values.[6] Furthermore, the risk of bleeding is also increased in these patients owing to impaired liver function, reduced platelet count and platelet dysfunction.[7] It is important to at least avoid any iatrogenic risks by always using an air filter for venous access
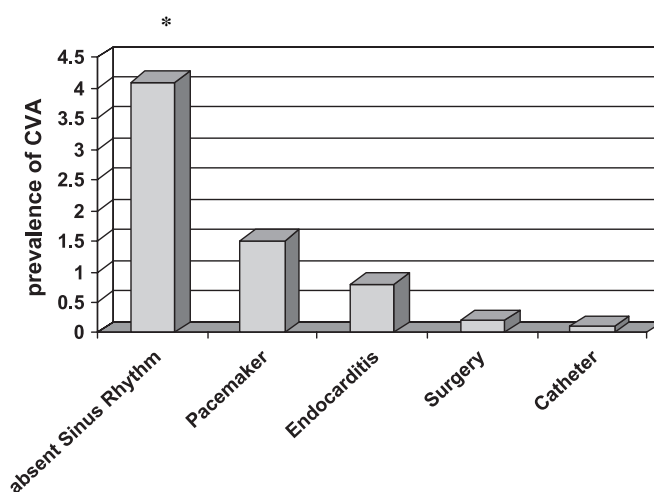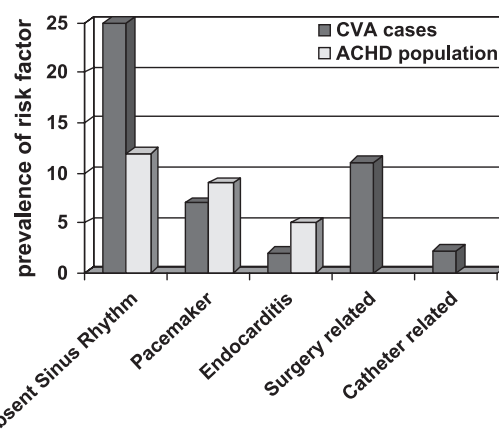
Figure 3 (Upper panel) Prevalence of risk factors in patients with CVA (dark bars) and in the entire ACHD study population where appropriate (bright bars). (Lower panel) Prevalence of cerebrovascular accidents in patients with risk factors. *p<0.0001 versus entire ACHD population. ACHD, adult congenital heart disease; CVA, cerebrovascular accident.

in cyanotic patients.[8] It is of note, however, that only one of the rare haemorrhagic CVA occurred while the patient was receiving anticoagulants.

Other cardiac conditions associated with a prevalence of CVA higher than average are mechanical prostheses, open ASD, Fontan, and atrial switch. Patients with open ASD tended to be older and arrhythmias were more prevalent in our patients with ASD, Fontan and atrial switch. CVA is a well-known complication in these circumstances, presumably due to extensive atrial pathology.[9] [10] Moreover, patients with pacemakers also tend to have more atrial arrhythmias, which further increases the embolic risk.[11]

In contrast, patients with closed septal defects had a lower than average stroke rate. No patient had a stroke during a follow-up of more than two decades in one published follow-up study of 135 patients with closed ASD.[12] This may not be true in cases of late ASD repair owing to the persistent risk of late atrial fibrillation.

Cardiac surgery, and to a far lesser degree, cardiac catheter procedures are additional factors of potential relevance. The latter have gained widespread application in ACHD in recent years, thus their impact on the occurrence of CVA may increase in the future. Absence of sinus rhythm is a known, important

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risk factor for CVA in older people, particularly in the presence of structural heart disease. Prophylactic oral anticoagulation is a strong indication in patients with CHD in the absence of sinus rhythm or presence of atrial fibrillation and flutter.[13]

The absolute numbers of CVA show a somewhat different picture. Most CVA cases occurred in patients with unrepaired ASD, who are also largely represented in the overall population. This may reflect a certain inclusion bias, since an ASD is detected in some patients during diagnostic investigation after a CVA, and thereafter this patient may be included in a database. Nevertheless, this over-representation does not detract from the fact that the relative stroke risk is much higher in the diagnostic categories mentioned above. In a recent study from Saudi Arabia, other important mechanisms of stroke in children apart from CHD were found to be dehydration, coagulopathy and vascular malformations.[14] In our cohort, thrombophilia was present in 2%, whereas a vascular malformation (hypoplastic vertebral artery) was reported in only one case.

In summary, our data show that CVA are a major cause of morbidity in this population of mostly young patients with CHD and absence of classical cardiovascular risk factors. Based on our experience, one out of 50 adult patients with CHD faces a CVA up to his or her middle life. The risk is doubled in several distinct circumstances and is even 10-fold higher in cyanotic patients.

Limitations

The major limitation is the retrospective nature of this study. Indeed inclusion criteria and definitions varied between the participating centres. There may be an underestimation of CVA because minor transient ischaemic attacks may not be mentioned in the case records or may remain unreported or even unnoticed by the patients themselves. CVA occurring in childhood may also be under-reported by the loss of such patients in adult databases. Including only cases with CVA occurring in the adult age range would, on the other hand, distort the results of such a survey, as many of the cases occurring in childhood lead to consequences lasting into adult life.

As a second flaw we are unable to provide detailed information about the exact aetiology and severity of CVA owing to a lack of detailed information in the databases. Imaging data (head CT or MRI) were available in only one-third of cases and since they were not recorded uniformly they were not analysed further. In addition, multivariate statistical analysis cannot be performed owing to the lack of a case-by-case entries for all patients. Mortality also was not analysed since death due to CVA was exceptionally rare in this series. Other causes of death were not within the scope of this study.

Nevertheless, these data are drawn from a large compilation of adults with CHD followed up systematically and highlight that CVA is a major contributor to the comorbidity in this predominantly young population.

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