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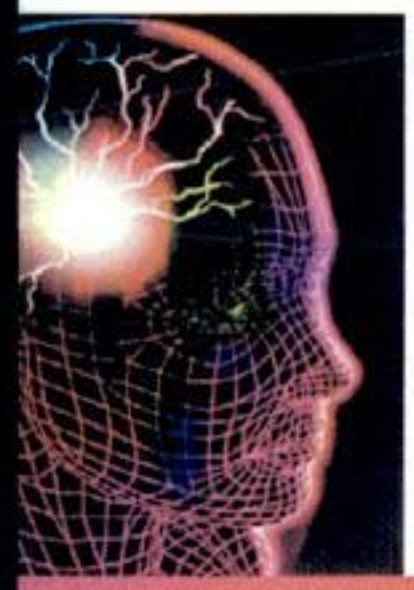

Women and Stroke Research

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WOMEN AND STROKE RESEARCH

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between 3.8 and 29 per 100,000 deliveries. The proportion of hemorrhagic and ischemic stroke is almost same during pregnancy. [7] Ischemic strokes account for 48% to 62% of all cerebrovascular accidents during pregnancy and intracranial hemorrhages occur in 38% to 51%. [5,7] Kittner et al examined cerebral infarction and cerebral hemorrhage separately and found no increased risk of ischemic stroke during pregnancy, but an 8.7-fold increased risk postpartum. They found a 2.5-fold increased risk of intracerebral hemorrhage during pregnancy and a 23.8-fold increased risk postpartum. [7]

The variables associated with pregnancy resulting higher incidence of stroke in women include higher parity; age more than 35 years, nonwhite race, and multiple pregnancies. [8,9,10] The medical factors predisposing to stroke are the same as in other young patients but more frequently observed during pregnancy include infections, diabetes, hypertension, pre-eclampsia and metabolic. [8,10] Risk factors, not previously reported, include lupus, blood transfusion, and migraine headaches. [11]

Vital statistics collected in England and Wales between 1938 and 1960 suggest that pregnancy has an effect as parous women have higher mortality from hypertension, ischemic and degenerative heart disease, and cerebrovascular disease than nulliparous women. [12] Maternal mortality rates are 0% to 38%, higher in intracerebral hemorrhage group. [13] The reported mortality associated with subarachnoid hemorrhage is 27% to 40%. [14] About 42% to 63% of survivors of pregnancy associated stroke have neurologic deficits. [13]

Pathogenesis

There is some relationship between occurrence of stroke and stage of pregnancy. Significant proportions of strokes occur during end of pregnancy and immediately after delivery. [13] Most arterial strokes presented in the third trimester and puerperium whereas venous infarction present in the puerperium. Subarachnoid hemorrhage can occur throughout pregnancy but intracerebral hemorrhage occurs after first trimester. Bleeding as a consequence of disseminated intravascular coagulation (DIC) occurs postpartum. [15] In one study the relative risk of 0.7 of cerebral infarction during pregnancy increases to 8.7 during the postpartum period. The relative risk of 2.5 of intracerebral hemorrhage during pregnancy increased to 28.3 during the postpartum period. [7] This suggests that significant hemodynamic alterations occurring with later stages of pregnancy and delivery are responsible for stroke. Arterial infarctions result from various causes like vasculopathy, cardiac embolism, and hematologic abnormalities.

Atheresclerosis and other Vasculopathies

Atherosclerosis though considered as disease of old people is seen in more than 20% patients of stroke younger than 40 years age and hence can be responsible for pregnancy associated strokes. The presence of risk factors causing early appearance of atherosclerosis like smoking, hypertension, diabetes, hyperlipidemia, and homocystinemia, should warrant possibility of stroke in pregnant women. [13] Arterial dissections accounting for 10% of

Drug	Category	
LMWH Clopidogrel	B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies which have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
tPA Heparin Nimodipine Mannitol	C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Aspirin	D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Warfarin	X	Contraindicated. Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

There are case reports of the use of intravenous rtPA to treat myocardial infarction, massive pulmonary emboli, superior vena cava syndrome and for the treatment of thrombosed valve prosthesis during pregnancy. [30,31,32,33,34]

Though tPA is shown to reduce morbidity and mortality of acute ischemic stroke, pregnant patients were excluded from the NINDS trial. The most recent guidelines for acute stroke management do not comment on pregnancy. [35,36]

There are 3 reports of rtPA use for acute ischemic stroke during the first trimester of pregnancy. In one report, using intravenous rtPA, the mother's neurological status initially deteriorated. [37] in the other, using arterial rtPA, maternal neurological status markedly improved. [38] Both women delivered healthy infants. In another report of thrombolysis in early pregnancy the patient improved clinically, did not develop complications after receiving rt-PA, and at 37 weeks' gestation, delivered a healthy infant, demonstrating that rtPA thrombolysis may be used safely in pregnant women. [39] There is one report of intra arterial thrombolysis in late pregnancy with favorable outcome. [40] Considering that rt-PA does not cross the placenta and taking into account that the complication rates do not exceed those of

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females may have a greater risk of death than males, but that this can be accounted for by other factors, such as older age or co-morbidities at stroke onset. In a similar analysis, Hankey et al. reported that female gender was not associated with death in multivariable analyses using 5-year outcome data from the Perth Community Stroke Study [3].

We have presented data demonstrating that worldwide more females than males die of stroke each year. There has been a reduction in mortality due to stroke over time and this decline was more rapid in females than in males. Among those with an incident stroke, the risk of death for males and females is similar in the acute period. In the longer term, females may be at a greater risk of death than males and this may be attributable to factors such as age.

The Prevalence of Stroke in Women

The gender-specific prevalence of stroke adjusted to the world population aged 65 years or over for various locations around the world is shown in Figure 1 [21, 29-34]. Females exhibited a lesser prevalence of stroke than males in all populations, except among the Indian population in Singapore. The lower prevalence in women is most likely attributable to lesser incidence. In some regions this may be attributable to a greater case-fatality in women; however this is not supported by the literature, as discussed above. The information gained from prevalence data is important as it can be used to allocate resources within the healthcare system and ensure that adequate support is available for those living in the community with stroke. The prevalence of stroke can be influenced by both the incidence of stroke in that population and the case-fatality among those who suffer a stroke.

The Incidence of Stroke in Women

Figure 2 shows the incidence of first-ever-in-a-lifetime stroke from 'ideal' stroke incidence studies that have been conducted around the world [17, 19, 20, 24, 25, 35-49]. There exist two comprehensive reviews of stroke incidence from high-quality studies; the first was conducted by Sudlow and Warlow [50] and the most recent review was by Feigin and colleagues [51]. Neither of these reviews were focused on the difference in incidence between males and females, although, both did include gender-specific data. The top panel of Figure 2 shows the gender-specific incidence rates of stroke adjusted to the European population aged 45 to 84 years. In general, females have a lesser age-adjusted incidence of stroke when compared to males. Similar incidence between males and females was found in Martinique in the French West Indies and in the Sicilian Aeolian Archipelago in Italy.

Age-adjusted incidence rates are useful because they enable stroke incidence to be compared around the world. However, because they are standardised to remove the effect of the age and gender structure of the population they came from, they do not give a true depiction of the burden of stroke within these communities.

Table 2. Change in stroke incidence for males and females in 'ideal' stroke incidence studies

Region	Mid-years of study periods	% change between studies		Comments
		Males	Females	
Auckland, NZ [13]	1981 – 1991	-9	8	Over total period: Males decrease, $p < 0.05$
	1991 – 2002	-7	-13	Females, NS due to increase 1981 - 1991 period
Espoo-Kauianen, Finland [16]	1973 – 1979	-33	-23	
	1979 – 1990	16	5	Net decrease over time periods
Fredriksberg, Denmark [53]	1973 – 1989	42	3	Males increase, $p < 0.01$; Females, NS
Framingham, USA [55]	1963 – 1983	-18	-6	Over total period: Males decreased, p *trend* < 0.02
	1983 – 1997	-15	-12	Females decreased, p *trend* < 0.01
Hisayama, Japan [14]	1967 – 1980	-48	-25	Males, $p < 0.05$; Females, NS
	1980 – 1994	-16	-13	Males and Females, $p < 0.05$*
Oxfordshire, UK [17]	1982 – 1986	-14	-9	Over total period: Males, RI 0.66 (95% CI 0.53 - 0.82) $p = 0.006$
	1986 – 2003	-23	-16	Females, RI 0.76 (95% CI 0.61 - 0.94) $p = 0.04$
Oyabe, Japan [52]	1979 – 1984	-25	-32	Males and Females, $p < 0.05$
	1984 – 1989	-8	2	Males and females, NS
Perth, Australia [15]	1989 – 1995	-30	-24	Males decrease, RR 0.70 (95% CI 0.54 - 0.90), Females - NS
Rochester, USA [56]	1982 – 1987	5	-4	Statistical significance not reported
	1977 – 1982	8	17	
Soderhamn, Sweden [23]	1976 – 1984	12	60	Males, NS; Females increase, $p < 0.05$
	1984 – 1988	-9	-4	Males and Females, NS
Tartu, Estonia [22]	1992 – 2002	-15	-20	Males, $p = 0.08$; Females, $p = 0.03$
Valle d'Aosta, Italy [54]	1989 – 1997	14	0	Males increase, $p < 0.05$; Females, NS

NS, not statistically significant; RI, relative incidence; RR, rate ratio. * Compared to 1st cohort with mid-year of 1967.

Table 4. Selected* case-control studies of oral contraceptive use and the risk of ischaemic stroke

Study (Years conducted)	Cases n	Controls n	OR (95% CI)	Adjustments	Dose-response	Comments
Haapiniemi et al. [71] (Not reported)	140	126	4.19 (1.74 – 10.11)	Age, BMI, hypertension, smoking, alcohol consumption	N/A	All ≤50μg EE_2
WHO collaborative study [72] (1989 – 1993)	697	1952	2.94 (2.23 – 3.88)	Hypertension, smoking, number of live births, education†	≥ 50μg oestrogen OR 5.3 (2.56 – 11.0) < 50μg oestrogen OR 1.53 (0.71 – 3.31)	Past users not at higher risk Interactions: OC use and smoking, hypertension, and migraine Type of progestagen not important – although few cases in some groups [89].
Schwartz et al. [73] (1991 – 1995)	60	485	1.37 (0.49 – 3.81)	Age, ethnic group, hypertension, smoking, diabetes, body mass index, alcohol consumption		All ≤50μg EE_2 Past use of OCs not significant
Siritho et al. [74] (1984 – 1996)	234	234	1.76 (0.86 – 3.61)	Smoking, alcohol, exercise, cholesterol, history of MI or TIA, hypertension, diabetes,		All ≤50μg EE_2 No interaction between hypertension or smoking and OC use Duration of OC use NS
Pettiti et al. [75] (1991 – 1994)	144	774	1.18 (0.54 – 2.59)	Treated hypertension, diabetes, smoking status, ethnic group, BMI		All < 50μg EE_2 Ever use versus no use - NS No interaction between OC use and smoking, age, hypertension or type of progestagen

Table 5. Studies of oral contraceptive use and the risk of haemorrhagic stroke

Study (Years of study))	Type of study	Type of haemorrhagic stroke	No. cases	No. controls.	OR/RR (95% CI)	Adjustments	Dose-response OR (95% CI)	Comments
WHO collaborative study [84] (1989 – 1993)	Case-control	All combined	1068	2910	Europe: 1.38 (95% CI 0.84 – 2.25) Developing Countries: 1.76 (95% CI 1.34 – 2.30)	Hypertension, smoking both regions Europe only: as above plus BMI	Europe: <50µg OR 1.27 (95% CI 0.70 – 2.32) ≥50µg OR 1.42 (95% CI 0.67 – 2.97) Developing countries: <50µg OR 1.66 (95% CI 1.16 – 2.37) ≥50µg OR 1.65 (95% CI 1.11 – 2.47)	Higher OR > 35 years versus < 35 years Evidence of interaction between OC use and smoking: CIs overlapped with non-smokers
Pettiti et al. [75] (1991 – 1994)	Case-control	All combined	151	774	Current versus non-current use: 1.14 (95% CI 0.60 – 2.16) Any use versus no use: 0.91 (95% CI 0.43 – 1.93)	Treated hypertension, diabetes, smoking status, race/ethnic group	Not reported	Progestagen type - Norethindrone and norgestrel: NS Other or unknown type: OR 4.64 (1.42 – 15.11) Evidence of minor interaction between OC use and smoking and OC use and older age: both NS

that these preparations are highly effective in managing their primary indications of contraception and menopausal symptoms and that both the risks and benefits of OCs and HRT should be considered when determining the appropriate treatment for an individual.

Incidence of Stroke During Pregnancy and the Post-Partum Period

A number of physiologic changes occur during pregnancy. These include an increase in plasma volume, creation of a thrombophilic state, an increase in insulin resistance, and immunosupression [102]. In some women these changes can lead to conditions such as gestational diabetes, preeclampsia, and arterial aneurysm [102]. These changes may predispose women to cerebrovascular disease.

Stroke incidence during pregnancy and during the 6-week post-partum period has been investigated in several settings. These estimates of stroke incidence range from 8.1 to 38.9 per 100,000 deliveries (see Table 7) [103-107]. The greatest incidence was observed in a tertiary hospital in Taiwan [105]. Following retrospective review of records, a total of 26 strokes occurred among women who were either pregnant or within 6 weeks post partum, during a 13 year observation period from 1992 to 2004. The least incidence was observed in a study conducted in France, being 8.9 per 100,000 deliveries [106]. Part of the reason for this lesser incidence in the French study may be that the observation period continued for only two weeks post-partum, thereby excluding those strokes that may have occurred out to 6 weeks post-partum.

Other authors have used routinely collected population morbidity data to assess the incidence of stroke during pregnancy and the post-partum period [108-110]. Using national hospital discharge survey data from 1979 to 1991, Lanska and Kryscio estimated that 8,918 cases of stroke occurred during pregnancy and the puerperium [108]. This translates to an incidence rate of 17.7 strokes (95% CI 14.7 – 21.3) per 100,000 deliveries. James and colleagues assessed a nationwide inpatient sample from 2000 to 2001 and found a greater incidence of stroke (34.2, 95% CI 33.3 – 35.1) in pregnant and post-partum women. It is likely that these investigators identified more strokes because, in addition to searching for pregnancy-related cerebrovascular events (International Classification of Diseases (ICD 9) code 674) [111], stroke diagnoses (e.g. ICD 9 codes 434 and 436) among people with pregnancy-related codes (ICD 9 codes 630-638) were also searched. This figure is similar to that reported in Sweden using individual record linkage between a nationwide inpatient register and birth register [109]. The strength of these studies is that a large number of cases were identified. However, their diagnostic accuracy is less reliable than in those studies where the investigators reviewed medical records in a systematic fashion. Despite this, there is some consistency between the estimates obtained using these different methods.

Interestingly, the incidence of ischaemic stroke and intracerebral haemorrhage were similar (Table 7) [103, 112, 113]. This is in contrast to non-pregnancy-related stroke where the incidence of intracerebral haemorrhage is approximately one quarter of that of ischaemic stroke [60]. Thus it appears that pregnancy selectively increases the risk of intracerebral haemorrhage.

clinical management. Although prior to menopause women have a lower risk of stroke than males, we have presented data highlighting that there are several instances in a woman's life where her risk of stroke increases. Taking OCs does heighten a woman's risk of stroke, but this must be considered in light of the prevention of unintended pregnancy and its associated risks. HRT, although initially believed to protect against CVD, appears to have no benefit for stroke prevention and may even increase the risk of stroke. For this reason, women are no longer prescribed HRT for the prevention of CVD. There is, however, increasing evidence that the timing of HRT is crucial and data from upcoming RCTs should help answer this important question. Finally, we have presented data on the risk of stroke during pregnancy and post-partum. While the absolute risk is low, the outcomes of these events can be devastating. In this review we have pooled data from good quality studies. An important note is that for many stroke incidence studies gender-specific data were not available. We highlight the need for investigators to present their data stratified by gender and to explore in detail the differences in stroke between males and females.

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Table 4. Specific CVD that only appears related to pregnancy or puerperium

• Eclampsia. • Choriocarcinoma. • Peripartum cardiomyopathy (PPCM). • Postpartum cerebral angiopathy (PCA). • Amniotic fluid embolism (AFE). • Air embolism (AE).

2.3. Pregnancies with CVD Risk

Pregnant women over 35 years are at a higher risk to present a CVD during the pregnancy or the puerperium [13,16]. Afro-American women are also more likely to develop CVD [11,12,16]. Multiparity does not increase the risk of CVD, but a higher frequency of CVT has been evidenced [15].

In univariate analysis, blood hypertension, myocardiopathies, cardiac valvulopathies, tabaquism, blood transfusions, migraine, pregnancy complications (infections, hydroelectrolitic and acid-base balance alterations), caesarean delivery, and hyperemesis gravidarum have been associated with CVD during pregnancy or puerperium [11,12,16]. However, in regression models only caesarean delivery (OR 3.5) and eclampsia/pre-eclampsia or other causes of hypertension during pregnancy (OR 13.9) independently predicted the presence of CVD [8,13,14,24]. It should be noted that caesarean delivery is usually recommended when a woman has a past history of CVD or has suffered a CVD during the pregnancy, to try to avoid and ICH due to the efforts associated with a vaginal delivery. Thus, the relationship caesarean-CVD could represent a confounder effect in retrospective studies [25]. Besides, disability and mortality rates of both mother with CVD and baby are not dependent on the type of delivery [21].

2.4. Aetiology of CVD During Pregnancy

The aetiology of CVD during pregnancy may be discovered in up to 75% of women [9,14,15]. We study later the aetiologies in each subtype of stroke.

2.5. Pregnancy Stages and Risk of CVD

The end of the third term (maximal risk over 2 days before delivery) and puerperium (mainly the first day after delivery) constitute the stages with a higher risk to develop a CVD [8,9,13,14].

(Figure 1), thrombotic thrombocytopenic purpura, or disseminated intravascular coagulation. Antithrombin III deficit, protein C deficit, prothrombin gene mutations, Leiden factor V, sickle cell anaemia, Sneddon syndrome, and homocystinuria should also be checked. The role of other coagulator factor, such, as Factor 11 and 12, are on research [35-38].

Cardioembolic causes: Pregnancy may predispose the recurrence of valvular rheumatic fever and thrombosis in mechanical valves. Primary prevention with antibiotic therapy to avoid endocharditis must be considered before the delivery in these cases. The presence of peripartum cardiomyopathy must be also borne in mind. The role of paradoxical emboli due to patent foramen ovale (PFO) [39-41] in conjunction with an increased risk of deep-venous thrombosis (DVT) and other prothrombotic states common in pregnant women, has not been already fully addressed. In pregnant women with IC or TIA and clinical suspicion of DVT or evidence of a prothrombotic disease [42,43], the presence of a PFO should be always ruled out, although it is not known if the techniques used for its diagnosis (transcranial Doppler or echocardiographic microbubble test) are safe for the foetus [44]. Percutaneous PFO occlusion has already been reported in pregnant women with CI due to PFO and paradoxical embolism [40,45-48].

Cerebral angiopathies Arterial dissections have been related to pregnancy by a hypothetic hormonal effect on the vascular wall, rather than on mechanical forces due to delivery work. Moreover, pregnancy may trigger an aggravation of concomitant systemic lupus erythematosus or Takayasu disease, leading to secondary vasculitis of the central nervous system. Cerebral angiopathy due to fribomuscular dysplasia or panartheritis nodosa have been also reported [3,8,26], and a specific angiopathy related to pregnancy known as post-partum angiopathy has also been described.

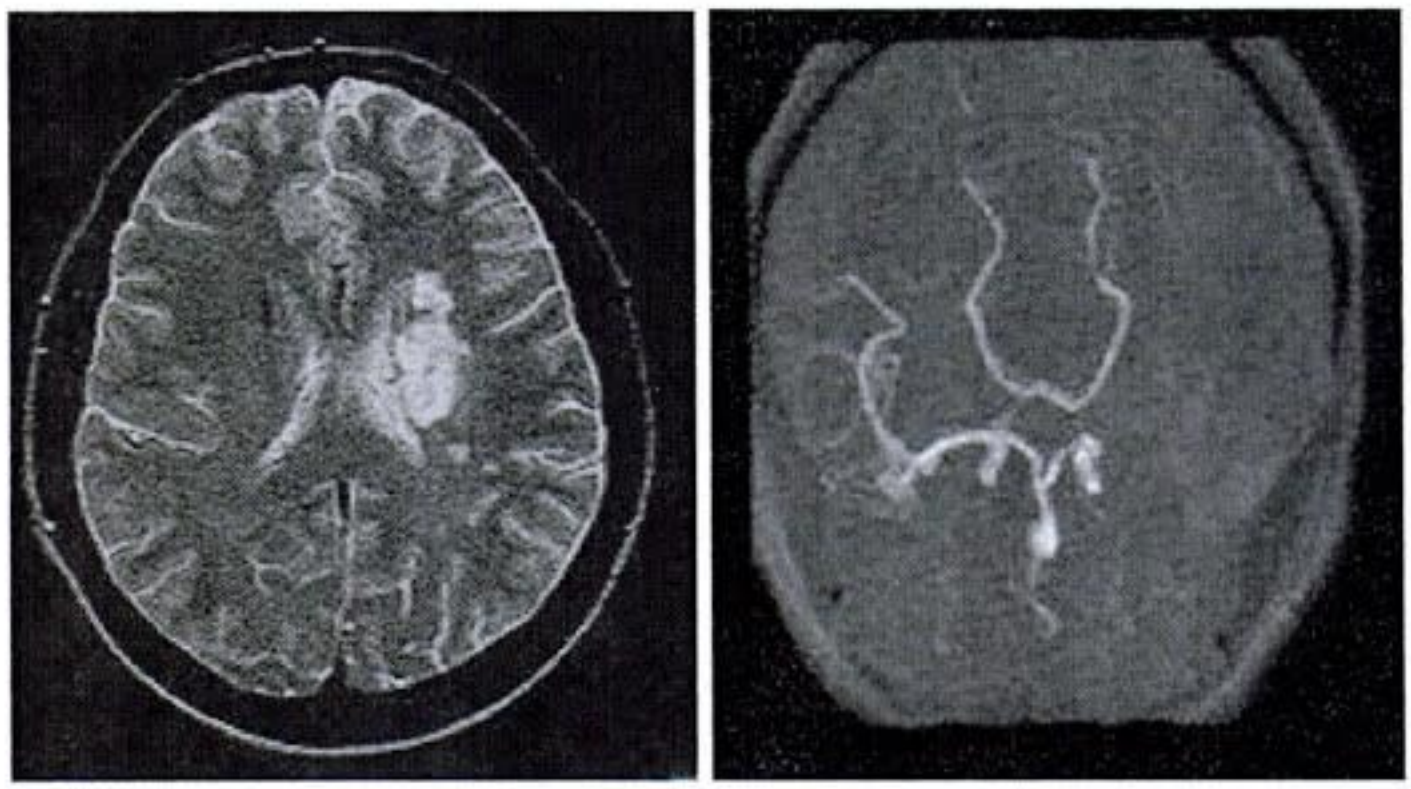

Figure 1. Puerperal woman of 28 years of age without known diseases. Her father suffered a lethal myocardial infarct when he was 43 years of age. Two weeks after a vaginal delivery without medical problems, she presented a sudden right hemiparesis and aphasia. MRI shows an ischemic cerebral infarct in the left middle cerebral territory (MCA). The angio-MRI shows a thrombotic occlusion of the proximal segment of the left MCA. Finally, the hypercoagulable states screening discover an antiphospholipid syndrome.

patients. Indirect signs, as sickle and tent reinforcement due to collateral venous regurgitation, and cerebral oedema, may be additionally present. Definite diagnosis must be done with venography by angio-resonance, helicoidal angio-CT, or conventional angiography.

4.6. Treatment

Treatment of CVT remains controversial in general population and pregnant women [71,72]. Treatment with sodium heparin is used since the forties, based on case reports of immediate complete remission. Heparin has been shown to decrease mortality in 14%, and disability in 15% of the patients. Moreover, it is a safe therapeutic option, even in CVT with associated hemorrhagic CI.

In DVT and PTE, LMWH has been shown to be as efficacious as sodium heparin. However, in CVT LMWH, as opposed to sodium heparin, has not demonstrated to be more efficacious than placebo [73,74], although it must be noted that pregnancy was an exclusion criteria in the two reported studies comparing LMWH versus placebo [73,74]. Recommendations on the use of sodium heparin in pregnant women do not differ from that developed for the treatment of CI, with minimal treatment duration of 3 months.

Local thrombolytic therapy by jugular or femoral catheterism (with urokinase or tPA) is used in CVT from the eighties. Preliminary evidence shows combined used of local thrombolysis followed by sodium heparin to be more efficacious than sodium heparin alone, although combined therapy is associated with a higher risk of haemorrhage (10%) [75]. A Cochrane meta-analysis does not currently recommend combined therapy, claiming more well balanced efficacy-safety studies to be performed [76]. One puerperial women was included in one study, but no pregnant women has been received this treatment up to date [75].

4.7. Prognosis

Maternal mortality associated with CVT during pregnancy is estimated in 0 to 20%. (Close to 0% in developed countries [9], and to 20% in least developed countries [69]). CVT recurrence is 6% in general population, but reported recurrence of CVT in pregnant women is close to 0% [64,77,78]. Since, prophylactic therapy with heparin is only recommended immediately after the delivery –during 1 month- in pregnant women with history of CVT and prothrombotic status. It could also be considered in women with past history of CVT unrelated to pregnancy, mainly if aetiology was not discovered.

Mortality of CVT tends to occur in elder patients, patients in severe coma, thrombosis in deep venous sinus or cerebellar veins, infectious or neoplastic aetiology, hemorrhagic infarct evidenced by CT, associated PTE, and seizures unresponsive to antiepileptic drugs [71]. CVT during pregnancy has a better prognosis than in general population [67]. Thus, 80% of the patients experience a complete remission or mild neurological impairment. An earlier

6. Specific Medical Entities

6.1. Eclampsia

Preeclampsia occurs when high blood pressure appears after week 20 of pregnancy, in a woman without past history of arterial hypertension, and that is solved over the three months after delivery [93]. Diagnosis of high blood pressure is done when blood pressure is higher than 140/90 mmHg, or when diastolic blood pressure increases more than 15-25 mmHg from values recorded before pregnancy. Preeclampsia affects 3% to 8% of pregnancies in the United States [94].

When seizures or decreases of the level of consciousness occur in the setting of preeclampsia, diagnosis of eclampsia is done. One out of 75 pregnant women with preeclampsia may develop eclampsia [945]. Eclampsia is associated with proteinuria (>0.5 g/24 hours), generalized or facial oedema, headache, visual disturbances (photopsies, cortical blindness), epigastralgia, and vomits [96]. The frequency of eclampsia is 1 / 2.000 pregnancies, and accounts for a mortality of 2% [97]. Eclampsia usually develops during the third term (50%), but it can appear during delivery (25%), or typically, over the 48 hours after delivery (25%).

Eclampsia is the responsible of 24-47% of CI, and 14-44% of ICH during pregnancy [7,11]; particularly, the risk of ICH starts when systolic blood pressure is higher than 155 mmHg [98].

MRI may show hyperintensities in T2 sequences, mainly in posterior cerebral regions (parietal or occipital area) paraventricular area or diffuse [99]. However, MRI in transient neurological deficits associated with eclampsia does not show alterations in diffusion-weighted sequences, which question their ischemic nature, and suggest a vasogenic oedema origin [100-103]. Echo-planar diffusion-weighted imaging is a new technique that can differentiate between cytotoxic and vasogenic oedema [104].

Prevention is the best treatment for eclampsia with careful supervision during pregnancy to early recognize a preeclampsia state. Obstetricians have usually guidelines to treat high blood pressure during pregnancy. Usually, antihypertensive treatment should be started in women with a systolic blood pressure over 160 mmHg or a diastolic blood pressure over 110 mmHg. The safer therapeutic options are intravenous labetalol, oral nifedipine and intravenous hydralazine. Atenolol, ACE inhibitors, angiotensin receptor-blockers and diuretics are avoided. The treatment of high blood pressure should be continued three months after delivery.

When eclampsia appears the management is multidisciplinary with involvement of the obstetric team, anaesthetics, haematology, and paediatrics. It seems that magnesium sulphate is the best drug in the prevention of seizures. Finally, the definitive treatment of eclampsia is delivery. HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), disseminated intravascular coagulation, renal failure and adult respiratory distress syndrome can appear as associated complications in eclampsia.

of the syndrome. Most AFE cases begin during the labour work during a vaginal delivery, but it can also occur during caesarean delivery (19%) and in the immediate postpartum (11%) [143-145].

Onset with shivers, nausea and vomits is followed by acute dyspnea, hypotension, hypoxia and cyanosis, decrease of the level of consciousness, and cardiorespiratory arrest within 1 hour in 50% of patients [143-145]. Seizures appear in 10-50%, but focal neurological deficits are very infrequent [26]. CI due to cerebral hypoperfusion or ICH due to disseminated intravascular coagulation may develop. Moreover, severe uterine atony, foetal bradycardia, and acute foetal distress are frequent comorbidities. Exclusion diagnosis is usually made, when pulmonary thromboembolism, air embolism, bronchoaspiration, septic shock, acute myocardial infarction, PPCM, anaphylaxia, and detachment of the placenta have been ruled out [143-145].

Chest radiography and ECG are usually normal. A blood analysis can be urgently done to study basic coagulation, fibrinogen, troponin, CK and D-dimer plus an arterial gasometry. Echocardiography and V/P pulmonary scintigraphy are advisable.

Detection of triptase or squamous cells in maternal pulmonary circulation is a specific marker. Other specific markers of AFE are: foetal antimucine TKH2 monoclonal antibody [146], coproporphirine zinc I (ZnCP I) [147], and levels of tissue factor or its inhibitors [148]. However, these markers are not still available in clinical practice.

AFE is an obstetric emergency that usually requires intensive care. Treatment comprises use of high doses of steroids, adrenaline, and dobutamine. Blood, plasma, and platelet transfusions may correct the coagulopathy. Uterine arterial embolization has been successfully used. Maintained monitoring of foetal constants must be done, and delivery must not be delayed. The best prophylactic treatment of this complication is to be alert of any parturient woman with dyspnea or psychomotor agitation during or shortly after delivery [143-145].

Maternal mortality due to AFE was 61-86% [139,142], but it has been reduced to 16-30% in the last years as a consequence of the advances in intensive care units [149,150]. Half of patients who survived to AFE may develop disseminated intravascular coagulation in less than four hours. Only 15% of women with AFE survive and do not have sequelae. In the other hand, 70% of newborns survive, but 39% with neurological sequelae, more severe with longer time intervals between cardiac arrest and delivery [141,150]. No data are available about the recurrence of AFE in future pregnancies.

6.6. Air Embolism (AE)

Clinical feature of AE are very similar to that of AFE. CI must be also present due to hypoperfusion, or due to arterial occlusion by aerial bubbles. Pulmonary thromboembolism or aerial systemic embolism may coexist with cerebral aerial emboli. Presence of 400-500 mL o air within the circulation may be lethal [151]. However, 97% of women with caesarean delivery show flow of aerial microbubbles in the precordial region, as assessed by ultrasonography [152,153]. AE is infrequent, and occur during delivery, especially during caesarean delivery [151,153,154]. If AE is suspected, the patients must be positioned left lateral decubitus, and a venous catheter must be introduced to extract aerial bubbles.

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Chapter 4

Oral Contraceptives and the Risk of Ischemic Stroke

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Abstract

Introduced in the late 1950s, combined oral contraceptives (OCs) are now used by hundred of millions of women worldwide and considered the most acceptable, effective, and most easily reversible method of contraception. In spite of their efficacy and ease of use, concerns about safety have persisted since the first case reports suggesting increased risk of thrombosis in the early 1960s. As a consequence of these observations, a large number of epidemiologic and clinical studies on the potential relation between OCs and risk of thrombosis were published, and the mechanisms of action of these compounds better elucidated. Based on the results of these studies, it is now generally accepted that the risk of cardiovascular events, including ischemic stroke, associated with OCs is higher in women with hypertension, smoking, or migraine. Accordingly, these conditions are considered contraindications to the use of OCs, particularly in women after age 35. However, OCs are still widely prescribed to women without these predisposing conditions but who have an increased risk for cardiovascular disease at baseline. Even a small degree of increased risk associated with OCs in the general population might be greatly amplified in such women and be highly clinically relevant.

In the present chapter we will discuss available epidemiologic data and mechanisms underlying the risk of thrombosis as a side effect of OCs use, as well as clinical

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had no effect on C-reactive protein, whereas oral oestrogen led to an increase [18]. These results are important because the trials that measured cardiovascular events used doses and formulations of estrogen that are typical replacement doses [19], and the effects of low-dose or non-oral estrogen on these outcomes are not known.

Effects on Endothelial Function

To investigate the effects of estrogen on endothelial function, blood-flow responses have been measured in women during various hormonal states. Endothelium-dependent vasodilation is greater (ie, improved blood flow) in premenopausal women than postmenopausal women [22]; for example, vasodilation varies with the high-estradiol phases of the menstrual cycle [23], and increases with estradiol replacement in postmenopausal women [24-27]. This beneficial vasodilatory effect with estrogen was shown in coronary vessels [28]. Measurements of endothelium-independent vasodilation have been less consistent, with some studies showing an increase with estrogen [23,27] and others showing no effect [24,25]. Estrogen replacement was also shown to increase the ratio of nitric oxide (potent vasodilator) to endothelin 1 (potent vasoconstrictor), thereby improving blood flow [29]. However, these beneficial vascular effects of estrogen were less apparent when measured in postmenopausal women with type 2 diabetes [30,31]. Overall, these studies suggest that estrogen generally has favourable effects on endothelial function, but this benefit can be attenuated in women with vascular risk factors. However, tests of physiological endothelial function are only a surrogate marker of estrogens' actions, and despite the promising evidence from animal and human studies, the randomised primary or secondary prevention trials have shown no benefit of hormone therapy for prevention of cardiovascular outcomes [20,21] or prevention of progression of coronary atherosclerosis [32]. The effect of estrogen on endothelial function in cerebral vessels has been studied primarily in the carotid arteries, and human studies have produced varying results. For example, carotid pulsatility index (a measure of impedance of distal blood flow) was negatively associated with transdermal-estrogen treatment in postmenopausal women, suggesting improved blood flow [33]. Hormone therapy increased carotid arterial compliance and distensibility coefficient, and lowered the stiffness index as measured by magnetic resonance imaging (MRI), an effect that was independent of changes in lipids and markers of inflammation [34]. By contrast, a randomised controlled trial of 17β-estradiol and gestodene (synthetic progestagen) in postmenopausal women showed no effect on carotid distensibility compared with placebo [35]. Measurement of the carotid intimal-medial thickness (IMT) with doppler ultrasonography is a surrogate marker of subclinical atherosclerosis and a prognostic marker of the risk of stroke. Cohort studies of IMT measurements have shown conflicting results with hormone therapy. In the Atherosclerosis Risk in Communities Study, menopause and hormone therapy had no effect on IMT progression [36]. By contrast, the Asymptomatic Carotid Atherosclerotic Progression Study showed a significant decrease in slowing of progression of IMT in women using estrogen-replacement therapy, especially in the absence of lipid-lowering therapy [37]. There have been two randomised studies of hormone therapy and carotid IMT measurement. In one study, women were assigned estrogen alone or

OCs were associated with an increased risk of stroke in young women. Although the currently prescribed estrogen doses are much lower than those in the early formulations, most of the case-control studies have shown a significant increased risk of stroke in users of OCs. The cumulative risk of stroke with OCs from all relevant studies published up to the year 2000 has been summarized in a first meta-analysis which demonstrated a 2.75 relative risk (RR; 95% CI, 2.24 – 3.38) associated with current use. Smaller estrogen doses were associated with lower risk, but risk was significantly elevated for all dosages [83].

One limitation of some studies included in the meta-analysis was that they did not control for traditional vascular risk factors (i.e., smoking), and they used hospital-based controls (rather than cohort design). According to the researchers who performed the meta-analysis, these should be considered an explanation for the higher risk estimates observed in such studies. Actually, the summary relative risk (RR) was slightly lower (RR 1.93; 95% CI, 1.35 – 2.74) for low-estrogen preparations in population-based studies that controlled for smoking and hypertension. This translates to an additional 4.1 ischemic strokes per 100 000 nonsmoking, normotensive women using low-estrogen OCs, or one additional ischemic stroke per year per 24 000 such women.

More recently, Chan and colleagues concluded from a meta-analysis of cohort studies that OCs did not result in an increased pooled risk ischemic and haemorrhagic stroke (OR 0.95; 95% CI 0.51 – 1.78) [84]. This conclusion contrasts with that of the previous meta-analysis [83], in which it was reported that the risk of ischemic stroke associated with low-dose OCs use in population-based, cohort studies was nearly doubled.

There are several reasons for the disparate conclusions between these two meta-analyses.

Both meta-analyses were based on available data from observational studies because no randomized controlled trials of OCs exist. A randomized design distributes both known and unknown confounding variables across the treatment arms, and therefore eliminates selection bias. However, it would be unethical to randomly assign active oral contraceptive treatment or placebo to women, so we are limited to results from observational studies. The quality of a meta-analysis is based entirely on the quality of the studies it combines. Differences among the included studies may also render their results incomparable, making an overall risk ratio invalid. Every study of OCs use and stroke risk to date has had methodological problems that could affect the conclusions drawn from meta-analyses. Some studies compared current users of OCs with non-current users, whereas others defined the control group as never-users. After the publication of early studies that showed a high risk of stroke associated with OCs use, the group of non-current users may have included women in whom use of OCs was deliberately discontinued because of higher underlying stroke risk factors.

Study outcomes have been defined as ischemic stroke only or as ischemic plus haemorrhagic strokes. A combined outcome is less suitable because ischemic and haemorrhagic stroke are etiologically distinct. In fact, data from a WHO study showed no association between haemorrhagic stroke and oral contraceptive use in young women [85]. Thus, the inclusion of haemorrhagic stroke in a study could substantially reduce the apparent association of stroke with OCs use. Most importantly, in the past, women who took oral contraceptive pills were more likely to smoke and drink alcohol. Thus, failing to control for these factors could lead to an overestimation of the effect of OCs use on stroke risk. More recently, however, oral contraceptive pills are prescribed mostly for women who are less

Table 2.Comparison of study design, characteristics and results of the 4 studies investigating the thrombophilia-oral contraceptives-ischemic stroke hypothesis

	Aznar et al. [109]	Slooter et al. [110]	Martinelli et al. [111]	Pezzini et al. [112]
Study design	case-control analysis	case-control analysis	case-control analysis	case-control analysis
No. of patients/controls	34/68	193/767	105/293	108/216
Patients				
Age (yrs, mean ± sd)	18 - 50	18 - 49 (38.6 ± 8.0)	fertile age (34.7 ± 9.1)	18 - 45 (33.9 ± 7.4)
Diagnosis	ischemic stroke	first ever ischemic stroke	first ever ischemic stroke	first ever ischemic stroke
Inclusion criteria	consecutive patients with cryptogenic stroke	consecutive patients with acute stroke	consecutive patients with history of stroke	consecutive patients with acute stroke
Exclusion criteria	atherosclerosis, heart disease, foramen ovale, vessel occlusive disease	TIA, cerebral venous sinus thrombosis, carotid artery dissection, history of cardiovascular or cerebrovascular disease, terminal illness, aphasia or cognitive impairment interfering with the questionnaire, not speaking Dutch		
Controls				
Age (yrs, mean ± sd)	< 50	18 - 49 (39.7 ± 7.7)	fertile age (34.9 ± 8.6)	34.6 ± 6.6
Selection criteria	not defined	from the general population by random digit dialing	from partners and friends who accompanied patients to the Center	from the hospital staff
Inclusion criteria	age-matched healthy subjects	age-matched subjects, no history of coronary heart disease, cerebrovascular event or peripheral vascular disease	healthy subjects of fertile age	age-matched subjects (± 3 years), no known history of vascular disease
Setting	Unit of Thrombophilia	Stroke Center	Thrombosis Center	Stroke Center
OC-users	not defined	within 1 month before the acute event	within the 2 weeks before referral	within 1 month before the acute event
Thrombophilic tests	FV G1691A PT G20210A	FV G1691A PT G20210A C677T MTHFR	FV G1691A PT G20210A C677T MTHFR hyperhomocysteinemia AT, PC, PS deficiency	FV G1691A PT G20210A C677T MTHFR
Risk of ischemic stroke	OCs + at least one thrombophilic defect OR, 14.27 95% CI, 0.66 - 309.99	OCs + FV 1691A OR, 11.2 95% CI, 4.3 - 29.0 OCs + MTHFR 677TT OR, 5.4 95% CI, 2.4 - 12.0	OCs + FV 1691A OR, 12.9 95% CI, 1.3 - 133.7 OCs + hyperhomocysteinemia OR, 6.2 95% CI, 1.7 - 22.0	OCs + at least one thrombophilic defect OR, 22.8 95% CI, 4.46 - 116.0 OCs + MTHFR 677TT OR, 8.87 95% CI, 3.72 - 21.1

FV, factor V Leiden; PT, prothrombin; MTHFR, methylenetetrahydrofolate reductase.

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subgroup analysis data from larger randomized trials is difficult to interpret, since the benefits of randomization are lost when these post-hoc analyses are completed.

It has also been speculated that women have different types of strokes and different types of risk factors. In multiple studies, it has been reported that men more frequently have hypertension, diabetes, hyperlipidemia, and obesity,[13] although other investigators have actually found that the reverse is true for some of these risk factors.[2,7] In an analysis of 1581 patients with first-ever stroke, women more frequently had cardioembolic strokes, whereas men had mostly atherothrombotic and lacunar strokes. [8]

Women tend to have less diagnostic workup and less thorough treatment for their risk factors. In the above described study of first-time stroke, the standard neurovascular workup was only completed in 66.7% of women, compared with 79.6% of men.[8] Multiple investigators have reported that high-risk women are less frequently treated according to appropriate lipid and blood pressure targets than are similarly high-risk men.[7,14]

Vascular risk is often assessed using a risk score based on a subject's age and presence of other vascular risk factors. The Framingham risk score, for instance, estimates 10-year cardiovascular risk and has been incorporated into some national guidelines.[15] This risk score based on the Framingham study data, however, may not apply in women who have different rates of vascular risk factors and who have less of an association between these risk factors and cardiovascular disease. This score has been criticized as underestimating risk in women, particularly due to the later presentation of cardiovascular disease in women.[15] Because of this, an independent risk score has been created, the Reynolds Risk score, based on data from women in the Women's Health Study. This score includes systolic blood pressure, C-reactive protein, total cholesterol, HDL cholesterol, glycosylated hemoglobin level in diabetics, and presence/ absence of smoking and family history.[16]

Aside from potential differences in standard vascular risk factors, women may differ from men in responsiveness to preventive medications, because of physiologic differences. Most of this is due to the presence of estrogen, which acts both as a neuroprotectant and as an antiatherogenic agent.[13] However, conditions where estrogen levels are elevated or otherwise manipulated, such as with pregnancy, oral contraceptive use, or postmenopausal hormone replacement therapy, may increase risk of stroke.

2. Aspirin in Stroke Prevention

A. Primary Prevention

The use of aspirin for primary prevention of stroke is one of the few areas where there are distinctly different recommendations and results in men versus women. The recently updated evidence-based guidelines for the prevention of cardiovascular disease now include a recommendation to consider aspirin for prevention of stroke in all women, depending on other risks and benefits.[11] This is primarily due to the recent publication of a randomized trial of aspirin in primary prevention specifically in women, the Women's Health Study.

The Women's Health Study was a randomized clinical trial, published in 2005. This study included 39,876 women aged 45 or older without prior cardiovascular disease who

were randomized to 100 milligrams of aspirin every other day versus placebo and were followed for 10 years. The overall relative risk reduction from aspirin was nonsignificant (RR 0.91, 95% CI 0.80-1.03) but the RR for stroke specifically was 0.83 (95% CI 0.69-0.99), with a RR of 0.76 for ischemic stroke (95% CI 0.63-0.93) and a nonsignificantly increased rate of hemorrhagic stroke in the women on aspirin. No difference was found in the specific endpoint of myocardial infarction.[17]

In a meta-analysis with gender-specific data, the point estimates for women were very similar to those reported above, because the majority of women were supplied by the Women's Health Study. Using aspirin for primary prevention, the RR for ischemic stroke was 0.76 (95% CI 0.63-0.93), again with no reduction in myocardial infarction but with a significant 12% reduction in the composite of cardiovascular events. These results are in contrast to the composite data from trials enrolling men. Of 44,114 total men, the use of aspirin for primary prevention led to 14% fewer cardiovascular events but no similar protection was found for the endpoint of stroke. Men on aspirin for primary prevention were 1.13 times as likely to have any stroke (0.96-1.33), with no effect on ischemic stroke (RR 1.00) and an increase of 69% on risk of hemorrhagic stroke (RR 1.69, 95% CI 1.35-2.20). The reduction of myocardial infarction in men was statistically significant. In general, women have strokes more frequently than they have myocardial infarctions, and men have myocardial infarction more often than they have strokes.[18]

In a separate analysis of the cost benefits of aspirin for primary prevention, a favorable cost-utility ratio was found (taking into account quality-adjusted life years) for older women with moderate or higher cardiovascular risk, but not in younger or lower risk women.[19]

Aspirin appears to be of benefit for primary prevention of stroke in women, although not for primary prevention of other coronary endpoints. Cost-utility analyses show the greatest potential benefit in moderate and high-risk older women.

B. Secondary Prevention

Men and women appear to have similar benefit from the use of long-term antiplatelet therapy in the secondary prevention of cardiovascular disease as a composite outcome.[20] There are formal recommendations to treat high-risk women with aspirin for the prevention of further cardiovascular events, or, in women who cannot take aspirin, to use clopidogrel.[11] However, these recommendations are aimed towards secondary prevention of cardiovascular disease in general. There have not been specific trials of women and secondary prevention of stroke with aspirin. In an analysis of the combined results of the Chinese Acute Stroke Trial and International Stroke Trial, two trials on the role of aspirin in early ischemic stroke with 20,000 subjects each, (which included 37% and 46% women, respectively), women did have less of an effect from aspirin than did men, although this interaction with gender was not statistically significant.[21]

In summary, men and women benefit from antiplatelet therapy for secondary prevention of stroke. Specific studies in women alone have not been done, but formal recommendations still support use of aspirin or other antiplatelet agents, if appropriate, in women.

C. Potential Mechanism of Sex-Specific Differences in Effect of Aspirin

The differences in responsiveness to aspirin based on gender may be due to hormonal effects on platelet aggregation.[13] Whereas testosterone has been found to activate platelet aggregation,[22] estrogen and/or progesterone act as an inhibitor of platelet aggregation.[23,24]

In addition, platelet resistance may vary in women versus men. In a study of aspirin and platelet function, women had more platelet reactivity at baseline and retained more platelet reactivity after being given 81 mg of aspirin for 14 days. However, most women (and men) given aspirin had appropriate complete suppression of the COX-1 pathway, as would be expected with the use of aspirin.[25]

3. Treatment of Hypertension

The AHA evidence-based guidelines for prevention of cardiovascular disease in women includes recommendations for pharmacotherapy if blood pressure is equal to or greater than 140/90, with a lower recommended threshold in the presence of concurrent renal disease or diabetes.[11] The INDANA (individual data analysis of antihypertensive intervention trials) study group performed a meta-analysis of the benefit of antihypertensives in women versus men. In general, women in the existing antihypertensive trials were older than the enrolled men, with higher baseline systolic blood pressure and higher cholesterol levels. The reduction in cardiovascular risk in women on antihypertensive therapy was not statistically significant for reduction of either total mortality or major coronary events, whereas a clear benefit was found for men for these endpoints. In addition, the use of gender as an interaction term was not found to be significant, but an interaction such as this necessitates a larger sample size. Regarding stroke, however, the odds ratio for women for having any stroke, comparing treatment with antihypertensives to placebo, was 0.62 (95% CI 0.52-0.73). The point estimate for men was an OR of 0.66, with a similar confidence interval.[26] Similar results are found when women were analyzed in different age groups: women over 55 years of age reduced their rates of any stroke by 38% (OR 0.62, 95% CI 0.53-0.73), with a reduction of 41% (OR 0.59, 95% CI 0.37-0.92) for all strokes in women under 55 who received antihypertensives, compared with those who got placebo.[27]

To summarize, women who receive antihypertensive therapy do appear to be protected from further stroke events, although less of an effect is present for prevention of other cardiovascular disease. Treatment of hypertension is thus formally recommended.

4. Treatment of Hyperlipidemia

Approximately 40% of women 65 and older have hyperlipidemia.[2] The evidence supporting use of medications (primarily statins) to reduce stroke risk is less clear in women. In general, women are included much less frequently in trials of statins. By 2004, 20,000 women had been enrolled in trials of statin medications, although they still only represented

25% of study participants.[7] These trials of statin therapy clearly show a benefit in reduction of ischemic stroke across the total population (men combined with women, leading to approximately a 17% total stroke reduction),[28] but because these studies primarily enroll men, it is less clear what the relationship is in women.[7]

Multiple authors have combined studies in an attempt to find a significant association between statin use and reduction in stroke or other cardiovascular endpoints in women. One such meta-analysis did report reduction in total cardiovascular disease events, which included stroke, by 20% in women who received statins (95% CI 0.71-0.91), but without separate significant effects for other specific stroke endpoints.[29] Other authors of randomized trials have also published subgroup analyses that have failed to show significant reduction of stroke in women on statins.[30] This has also been the case in studies where nonrandomized use of statins was analyzed: in the HERS trial (Heart and Estrogen/ progestin Replacement Study), use of statins was reviewed and women who used statins had less combined cardiovascular disease (Hazard rate 0.79, 95% CI 0.63-0.99) but stroke or TIA was not significantly reduced (HR 0.96, 95% CI 0.71-1.29).[31]

The data on the use of statins do support use of statins generally for the prevention of stroke (regardless of gender) and support use of statins for prevention of combined cardiovascular endpoints in women. There is not clear evidence, however, specifically supporting the use of statins in women for the prevention of stroke.

5. Diabetes Mellitus

The Nurses Health Study followed 116,316 women who were 30 through 55 years of age at the study onset in 1976. In this population, followed for over 25 years, both type I and type II diabetes were strongly associated with risk for stroke.[32] Diabetes remains a major risk factor for cardiovascular disease, and the subset of women with diabetes are the one subgroup who have not had improvements over time in cardiovascular-related mortality.[7]

Data from the Framingham study have suggested that diabetes is a more potent risk factor for cardiovascular disease in women than in men. After adjustment for other vascular risk factors, the impact of diabetes on development of stroke, in particular, is the same for men and for women, but remained greater for death from cardiovascular disease in women.[33]

The metabolic syndrome (which includes insulin resistance or glucose intolerance as a component, in addition to abdominal girth, hypertension, and dyslipidemia) is highly prevalent in American women. Whereas the prevalence of the metabolic syndrome has only increased by 2.2% in men from the late 1980's to the late 1990's, women have increased their age-adjusted prevalence by 23.5% in the same decade. Women with the metabolic syndrome also have a higher risk of cardiovascular disease than do men, although it is a risk factor in both groups (RR 2.10 in women, versus 1.57 in men).[7]

Diabetes and the associated metabolic syndrome clearly increase risk for cardiovascular disease, including stroke. Because of this, the AHA guidelines for cardiovascular disease prevention in women recommends use of lifestyle changes and pharmacotherapy to maintain

a glycosylated hemoglobin less than 7% in all women. Having diabetes places a woman in the high-risk category in decisions regarding other risk factor modification.[11]

6. Atrial Fibrillation

Evidence about the prevalence of atrial fibrillation in women versus men is somewhat inconsistent; while some authors report a lower frequency in women (5 per 1000 in women versus 8 per 1000 in men),[34] the Framingham data indicate that 1.7% of women have atrial fibrillation and have a 1.5 times higher risk of developing atrial fibrillation than their male counterparts.[34,35]

The risk of stroke, however, does seem to be higher in women with atrial fibrillation than in men with atrial fibrillation.[34,36] In the Renfrew/ Paisley study, 30% of women with atrial fibrillation had a stroke, compared with only 17% of men with atrial fibrillation. The relative risk of stroke is 5.5 in women with atrial fibrillation (95% CI 3.3-9.2), whereas for men it was only 2.1 (95% CI 1.1-4.3).[37] This applies particularly for men and women who are not on anticoagulation (RR 1.6 for men versus women, 95% CI 1.3-1.9). In an analysis of the subjects in the SPAF trials (Stroke Prevention in Atrial Fibrillation) who received aspirin or were not fully anticoagulated and had an INR<1.4 (the study included an arm of subjects receiving aspirin plus low-dose warfarin), female sex was independently associated with higher risk of stroke (RR 1.6).[38] Because of the higher risk of stroke, the Framingham risk score adds additional points to an individual's stroke risk with atrial fibrillation if she is female.[35]

Because stroke risk is higher in women with atrial fibrillation, choice of treatment is critical. In the ATRIA (The AnTicoagulation and Risk factors In Atrial fibrillation) study, women on warfarin had a RR for combined thromboembolic endpoints of 0.4 (95% CI 0.3-0.5) compared with men, who had a RR of 0.6 (95% CI 0.5-0.8). Hemorrhage rates did not differ between men and women.[36]

Women tend to be undertreated for atrial fibrillation, and practitioners tend to be more reluctant to prescribe anticoagulant therapy to elderly women in particular.[34] There is no evidence supporting this practice, but there is evidence supporting the importance of prevention of stroke with anticoagulation, particularly in women.

7. Treatment of Carotid Artery Disease

Women have lesser carotid artery wall thickness than do men.[39] Between 5-7% of women aged 65 and older have over 50% carotid stenosis, compared with 7-9% of men.[40,41] In addition to these differences, management recommendations, both for symptomatic disease and asymptomatic disease, may differ in women.

In pooled data from the NASCET (North American Symptomatic Carotid Endarterectomy Trial) and the ECST (European Carotid Surgery Trial) trials, outcomes and complications in 1718 women with symptomatic carotid disease were analyzed. Men had the

greatest benefit from surgery overall, and women had higher rates of perioperative stroke and death (OR 1.5, 95% CI 1.14-1.97). The number needed to treat with surgery to prevent one ipsilateral stroke was 9 in men and 36 in women.[42] However, this applied to patients who underwent surgery for over 50% stenosis. When extent of stenosis was further subdivided, a clear benefit was seen in women with over 70% stenosis (an absolute risk reduction from surgery of 9.9%) but not in women with 50-69% stenosis. In addition, the timing of surgery is even more important in women than in men. Both men and women benefit more if surgery is performed within 2 weeks of the latest TIA or minor stroke, but this is particularly the case for women, for whom the benefit from surgery decreases more rapidly with extended time.[43]

In the major asymptomatic carotid artery treatment trial, ACAS (Asymptomatic Carotid Atherosclerosis Study), women with over 60% stenosis who underwent surgery were not found to have a significant reduction in stroke (17% nonsignificant risk reduction), even though a significant finding was reported in the overall population (men had a 66% relative risk reduction). It is likely that this lack of effect in women in this trial is due to the higher rates of perioperative complications in women (3.6% versus 1.7% in men).[44] The complication rates in ACAS, however, have been criticized as being particularly low, and thus may not be generalizable to any other populations. Nonetheless, even in other studies reporting more uniformly accepted operative complication rates, women had higher perioperative complication rates (5.3% in women, versus 1.6% in men, p=0.02).[45] The reasons for this are not entirely clear.

In conclusion, regarding symptomatic carotid artery disease, women have less benefit from carotid endarterectomy than do men, but surgery does remain superior to medical therapy for women with over 70% stenosis. Benefit from surgery is greatest in women in the initial 2 weeks after a TIA or nondisabling stroke. There is no support of the standard use of endarterectomy for women with asymptomatic carotid stenosis.

8. Lifestyle Modifications and Nutritional Supplements

In the Women's Health Study, women who had a healthy lifestyle (including not smoking, with a healthy diet, maintenance of ideal weight, and a regular exercise regimen) had lower rates of total stroke (HR 0.45, 95% CI 0.24-0.83) and ischemic stroke than women without these healthy habits. Hemorrhagic stroke, however, was not decreased in women with this dichotomized healthier lifestyle.[46] This study, however, was not randomized with regards to lifestyle factors. Similar results regarding smoking and obesity as risk factors for stroke have been reported in the 117,006 women in the Nurses Health Study, and women in the Copenhagen City Heart Study, as well.[47-49]

There have not been data supporting the use of vitamin supplements in the prevention of stroke in women. In two randomized studies assessing potential benefit from Vitamin E (the Women's Health Study and the Women's Antioxidant Cardiovascular Study), there was no decrease in rate of stroke or other cardiovascular events in women who received Vitamin E.[50,51]

The American Heart Association does formally recommend maintenance of a healthy lifestyle, recommending smoking cessation, heart-healthy eating, regular physical activity, and weight management.[11] There are no clear benefits of other nutritional supplements in the prevention of stroke.

9. Estrogen in the Prevention of Stroke

The controversy regarding the cardiovascular risks associated with hormone-replacement therapy is not the focus of this chapter. However, a brief discussion is appropriate in any discussion of stroke prevention in women. In prior years, based on observational studies, hormone-replacement therapy was considered to be useful preventive therapy for women at risk of cardiovascular disease.[52] This practice changed, however, with the publication of the Women's Health Initiative. In this randomized trial, the combination of estrogen plus progestin was compared to placebo, and the hormone supplementation group was found to have an *increased* risk of cardiovascular disease, and stroke in particular. The hazard ratio for combined hemorrhagic and ischemic strokes was 1.33 (95% CI 1.02-1.68) in women who were on the estrogen replacement.[53] To assess the potential benefit of raloxifene (a selective estrogen-receptor modulator), Barrett-Connor and colleagues performed a randomized trial in postmenopausal women with cardiovascular disease or multiple risk factors for cardiovascular disease. They found no significant difference in total stroke but a slight increased risk in fatal stroke (HR 1.49,95% CI 1.00-2.24) in women who received raloxifene.

Estrogen therapy does not appear to function as protective for stroke, despite laboratory findings supporting its role as a neuroprotectant and antiatherogenic agent. In addition, its use may even increase risk for stroke. This is consistent with observational findings supporting an increased risk of stroke in women on oral contraceptives[2,13] Pregnancy is also a clearly established risk for stroke, and leads to the increased rates of stroke in women of child-bearing age, compared to men in the same age group. Because of these different risk factors in women, consideration of appropriate stroke secondary preventive therapies will vary depending on the exact circumstances regarding a woman's prior stroke. For instance, a woman who has a stroke during pregnancy due to cerebral venous sinus thrombosis will need to take appropriate preventive measures (with low-molecular weight heparin, for instance) in subsequent pregnancies. Similarly, women who develop strokes while on oral contraceptives without another clear cause are advised to discontinue oral contraceptive therapy.

Conclusion

Stroke is a significant cause of morbidity and mortality in women: women tend to have more strokes than myocardial infarctions, whereas the reverse is true for men. In general, women are treated with similar preventive therapies as are men, in primary and secondary prevention of stroke. However, most studies primarily enroll men, and because of this and the fewer endpoints in the fewer women enrolled, most subgroup analyses of the women enrolled

in these studies fail to find statistically significant differences. The recent publication of the Women's Health Study, which shows that women have decreased rates of stroke but not coronary disease when aspirin is used for primary prevention, which is direct opposition to the findings from studies of men, pinpoints the importance of randomized trials dedicated specifically to women.

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Chapter 6

Carotid Endarterectomy—High-Risk Factors and Hyperperfusion Syndrome

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Several randomized clinical trials have confirmed the effectiveness of carotid endarterectomy (CEA) to prevent stroke in patients with symptomatic and asymptomatic carotid stenosis. The first epoch-making randomized clinical trial, North American Symptomatic Carotid Endarterectomy Trial (NASCET) was published in 1991 (43). Since then, a number of multicenter randomized clinical trials, retrospective population- and large institution-based studies and case series studies have been reported. In this article, we focus several topics on major developments since 1991. At first, we review so-called "high-risk" CEA in consideration of carotid artery stenting (CAS). Second, we compare local and general anesthesia for CEA. Third, we discuss shunt and monitoring system for cerebral ischemia. Although last but not least, we review hyperperfusion syndrome.

The High-Risk Patient for Carotid Endarterectomy

A review of the recent literature demonstrates a low postoperative stroke or death rate after CEA. On the other hand, high surgical risk is advocated as a major criterion for CAS (68). However, the low stroke or death rate of CEA in recent series compounds the difficulty in defining the "high-risk" patients. To date, the definition of "high-risk" patients for CEA has been elusive (41). Before reviewing CEA studies, we summarize the results of the recent CAS studies. There are three latest CAS studies, i.e., the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial (68), Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial (35) and Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial (60).

CAS Studies

Early results with CAS have been quite variable, reflecting the heterogeneous patient populations studied. Recently, however, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was reported, which was the first completed controlled, prospective randomized trial comparing CEA and CAS with cerebral protection (68). Only "high-risk" patients (n = 334) were enrolled in the SAPPHIRE trial. Criteria for "high-risk" in this study included: clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal-nerve palsy, previous radical neck surgery or radiation therapy to the neck, recurrent stenosis after endarterectomy, and age >80 yr. The cumulative incidence of stroke, death, and myocardial infarction within 1 year (12.2% versus 20.1%), as well as the cumulative incidence of cranial-nerve palsy and revascularization and the length of the hospital stay, were lower in CAS group than in CEA group among high-risk patients. They concluded that CAS with the use of an emboli-protection device is not inferior to carotid endarterectomy. However, no statistically significant difference in the periprocedural (30-day) risk of stroke (CAS 3.6% versus CEA 3.1%) and mortality (CAS 1.2% versus CEA 2.5%) were found between CAS and CEA in the study. More patients suffered from 30-day myocardial infarction (MI) in CEA group (6.1%) than in CAS group, but there was no statistically significant difference between the two groups. When taken together, the 30-day stroke-death-MI rate in CAS was 4.8% compared with 9.8% in the CEA group (P = 0.09). Most of this difference was accounted for by non-Q-wave MIs detected on routine perioperative troponin I assessments. This high 6.1% incidence of MI in the CEA group has not been seen by other groups (40). In addition, the implication of the non-Q-wave "chemical" MI is not uncertain. Although some suggest that even minor perioperative elevations in troponin I increase 6-month mortality (not perioperative mortality), one should not necessarily conclude that the CEA reduces one's life expectancy. Instead, it may identify patients with significant coronary disease that were not identified preoperatively by stress testing or other forms of risk stratification (8).

The patient characteristics in SAPPHIRE trial were different from that in the carotid surgery trials. Fewer than 30% of patients with carotid stenosis were symptomatic and more than 70% were asymptomatic. This means that only 96 symptomatic patients were included in SAPPHIRE trial. For symptomatic patients, the 30-day stroke-death-MI rate was larger in CEA group (9.3%) than in CAS group (2.1%), but the difference was not statistically significant. At the end of 1 year, the cumulative incidence of primary end points (stroke-death-MI) in the symptomatic patients was 16.8% in the CAS group and 16.5% in the CEA group. This means that most of major adverse clinical events occurred during the follow-up period after therapeutic intervention for CAS group. In the asymptomatic patients the risks appeared to be even higher, which goes against usual experience, with up to a 21.5% risk of a primary end point at 1 year in the CEA group and 9.9% in the CAS group. The 30-day stroke-death-MI rate was larger in CEA group (10.2%) than in CAS group (5.4%), but the difference was not statistically significant. These complication rates are not acceptable for treating asymptomatic patients where the chances of ipsilateral stroke are generally low and

where there should be 3% peri-procedural risk (17, 24), although this study included only "high-risk" patients.

More recently, two noninferiority trials including only symptomatic carotid stenosis were reported to show that CAS is not worse than CEA. The Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial—a French study—compares CAS with CEA in patients with symptomatic carotid stenosis of at least 60% (35). The trial was stopped prematurely after the inclusion of 527 patients because the 30-day incidence of any stroke or death was 3.9% after CEA and 9.6% after CAS, a significant difference ($p = 0.01$). At six months, the incidence of any stroke and death was 6.1% after CEA and 11.7% after CAS, again, a significant difference ($p = 0.02$).

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial—German–Swiss–Austrian study—included 1183 patients (60). The rate of death or ipsilateral ischemic stroke from randomization to 30 days after the procedure was 6.84% with CAS and 6·34% with CEA. The one-sided p value for non-inferiority is 0.09. As a conclusion, SPACE failed to prove non-inferiority of CAS compared with CEA for the periprocedural complication rate.

In contrast to SAPPHIRE trial, both studies found that CAS was not 'as good as' CEA, while EVA-3S found CEA to be statistically superior. Given that both trials failed to prove the non-inferiority of CAS compared with CEA in the first 30 days, CAS for symptomatic carotid stenosis might be restricted to patients with contraindications to surgery and those participating in randomized clinical trials. It seems to be necessary to improve the safety of CAS before it can become an alternative to CEA in patients with symptomatic carotid stenosis. Since the methodologies of these three studies differed from each other in many respects, these trials have courted considerable controversy in both of pro-CAS and pro-CEA lobbies. Surgeons in the pro-CEA lobby might think that SPACE and EVA-3S have settled the debate and restored CEA to primacy. Many ardent critics in the pro-CAS lobby tend to dismiss them as being methodologically problematic and unrepresentative of contemporary CAS practice, particularly from the view of interventionalist experience and use of cerebral protection devices (19, 42). However, both therapies have a complementary role. More data are required to clarify how the two therapies can complement each other. Therefore, we should wait for the results of the two remaining trials that are randomising recently symptomatic patients, i.e., Carotid Revascularization Endarterectomy vs. Stenting Trials (CREST) and International Carotid Stenting Study (ICSS).

CEA studies

In analysis of pooled data of symptomatic carotid stenosis from the European Carotid Surgery Trial (ECST), NASCET, and Veterans Affairs trial, 7.1% of patients had strokes or died within 30 days of surgery (55). Operative risk did not differ between the stenosis groups. The risk of death within 30 days of endarterectomy was 1.1%.

In asymptomatic carotid atherosclerosis study (ACAS), perioperative stroke/death rate was 2.3% (17). In Asymptomatic Carotid Surgery Trial (ACST), stroke or death within 30 days was 3.1% (24). These randomized clinical trials (RCT) included patients who had only

good medical risk. Exclusion criteria of these RCTs include octogenarians, myocardial infarction (MI) within 6 months, unstable angina, lung failure, renal failure, uncontrolled hypertension, and uncontrolled diabetes mellitus. Therefore, small portion of whole patients who underwent CEA participated those RCTs. These exclusions have been used to criticize the validity of the conclusions of the trials.

Population-based studies have been traditionally used to clarify the validity of selective RCTs in the real world. In retrospective analyses of data on Medicare beneficiaries aged 65 years and older in the United States, the mean 30-day mortality significantly decreased from 1991 (1.95%) to 1995 (1.44%) and from 1995 to 2000 (0.89%) (59). Ontario Carotid Endarterectomy Registry reported that the overall 30-day death or stroke rate after surgery was 6.0% in 6038 CEAs between 1994 and 1997 (64). A history of transient ischemic attack (TIA) or stroke (odds ratio [OR], 1.75), atrial fibrillation (OR, 1.89), contralateral carotid occlusion (OR, 1.72), congestive heart failure (OR, 1.80), and diabetes (OR, 1.28) were significant independent predictors for 30-day death or stroke. Stoner et al analyzed the prospective National Surgical Quality Improvement Program (NSQIP) database (62). They described isolated 13622 CEAs between 2000 and 2003 at 123 Veterans Affairs and 14 private sector academic medical centers. The composite stroke, death, or cardiac event rate was 4.0%; the stroke/death rate was 3.4%. Significant multivariate correlates of the composite outcome were as follows: deciles of age (OR, 1.13), insulin-requiring diabetes (OR, 1.73), oral agent-controlled diabetes (OR, 1.39), decade of pack-years smoking (OR, 1.04), history of transient ischemic attack (OR, 1.41), history of stroke (OR, 1.51), creatinine >1.5 mg/dL (OR, 1.48), hypoalbuminemia (OR, 1.49), and fourth quartile of operative time (OR, 1.44). Cardiopulmonary comorbid features did not affect the composite outcome in this model. Regional anesthesia significantly reduced the composite outcome (31%; OR, 0.69). These population-based studies confirmed a low postoperative stroke or death rate that had been demonstrated in the RCTs.

Large institution-based studies were also important to clarify the validity of RCTs. Ouriel et al described 3061 CEAs during a 10-year period at Cleveland Clinic (48). A high-risk patient subgroup was identified, defined by the presence of severe coronary artery disease, chronic obstructive lung disease, or renal insufficiency. The rate of the composite end point stroke/myocardial infarction (MI)/death was 3.8% (stroke 2.1%, myocardial infarction 1.2%, and death 1.1%) in the total group. Among the high-risk subset, the composite end point stroke/MI/death occurred in 7.4%. This rate was significantly greater than the corresponding rate of 2.9% in the low-risk subset. Similarly, the rate of stroke (3.5% versus 1.7%) or death (4.4% versus 0.3%) was significantly greater in high-risk patients. Gasparis et al reported on 788 isolated CEAs between 1996 and 2001 (22). High-risk comorbidities included: age 80 years or more, angina, heart failure, MI 6 months or less, steroid-dependent or oxygen-dependent pulmonary disease, and creatinine level of 3 or more. Anatomic high risk was defined by: contralateral occlusion, lesion above C2 or requirement of digastric division, reoperation, and neck radiation. Twenty-nine percent of CEAs was classified as high-risk. The total stroke and death rate was 1.1% for all. There was no significant difference of stroke and death rate between the high-risk group (1.3%) and the normal-risk group (1.1%). In contrast to the results at Cleveland Clinic, they stated that patients with significant medical comorbidities, contralateral carotid occlusion, and high carotid lesions could undergo

operation without increased complications. Mozes et al retrospectively reviewed consecutive patients who underwent CEA between 1998 and 2002 at Mayo Clinic (40). Of 776 isolated CEAs performed, 323 (42%) were considered high risk that was defined on the basis of similar criteria. The overall postoperative stroke rate and mortality rate was 1.4%. Comparison of high-risk and low-risk CEAs demonstrated no statistical difference in the stroke rate. Factors associated with significantly increased stroke risk included cervical radiation therapy (OR, 15), class III or IV angina (OR, 11), symptomatic presentation (OR, 3.3), and age 60 years or younger (OR, 7.7). Overall mortality was 0.3%, not significantly different between the high-risk (0.6%) and low-risk groups (0.0%). Non-Q-wave MI was significantly more frequent in the high-risk group than low risk group (3.1 versus 0.9%). They stated that CEA could be performed in patients at high risk, with stroke and death rates well within accepted standards. Pulli et al reported a posthoc analysis on 1883 CEAs in 1554 patients between 1996 and 2001 (51). The cumulative 30-day stroke and death rate was 1.3%. Univariate analysis and logistic regression did not show statistical significance for 30-day results in any of the considered variables such as age, sex, clinical symptoms, anatomic features, cardiac, renal and pulmonary disease. They stated that CEA is a safe procedure also in so-called high-risk subsets of patients.

These data question the extensive concept of high-risk CEA, based merely on exclusion criteria in the NASCET and ACAS trials. If a high-risk group exists, it is small and restricted to certain individual risk factors. For resolution of this question, these factors should be focused.

Age

In NASCET, the perioperative (30-day) risk of stroke and death at any degree of stenosis was 5.2% for 75 years or older group (n = 172), 5.5% for 65-74 years (n = 635), and 7.9% for less than 65 years (n = 608) (2). The oldest group not only had the lowest stroke and death rate but also obtained the greatest benefit from CEA. Among patients with 70-99% stenosis, the absolute risk reduction of ipsilateral ischemic stroke at 2 years was 28.9% for patients aged 75 years or older, 15.1% for those aged 65-74 years, and 9.7% for the youngest group. Among patients with 50-69% stenosis, the absolute risk reduction was significant only in those of 75 years and older (n=145; 17.3%). For asymptomatic patients, the perioperative (30-day) risk of stroke and death rate was 3.7% for 75 years or older group (n = 326), 2.9% for 65-74 years (n = 815), and 2.9% for less than 65 years (n = 509) (24). There was no significant difference in the stroke and death rate among the three groups. In contrast to symptomatic patients, however, the benefits at 5-year from CEA were definite for the two younger groups but uncertain for the oldest group in asymptomatic patients.

Most RCTs have excluded patients older than 80 years, suggesting that they are either at higher procedural risk or have decreased life expectancy. Several large retrospective studies have been conducted to determine if age of 80 years or more is related to increased morbidity and mortality in patients undergoing CEA.

The Ontario CEA registry reported that the overall 30-day death or stroke rate after surgery was 6.7% in patients aged 75 years or older (n = 1455) and similar value (6.2%) in

those aged 65-74 years (n=2782) (64). In contrast, the analysis based on the NSQIP database demonstrated that 30-day death or stroke rate in patients aged 80 years or older (4.5%, n = 1341) was significantly higher than that in patients aged less than 80 years (3.2% n = 12281) (62). In a retrospective review on Maryland Health Services Cost Review Commission (MHSCRC) database, 9918 elective CEAs were performed between 1990 and 1995 (49). Postoperative death and neurologic complications occurred in 90 (0.9%) and 166 (1.7%) cases, including 0.8% and 1.7%, 0.9% and 1.6%, 0.9% and 1.8%, and 1.4% and 1.3% of patients < 65 years, 65 to 69 years, 70 to 79 years, and > or = 80 years old, respectively. Miller et al described 2217 CEAs in 1961 patients between 1993 and 2004 (37). In patients aged 80 years or more (n = 360), compared with their younger cohort (n = 1857), there was no difference in stroke (1.1% versus 0.8%, P = .333) but there was a higher operative mortality (1.9% versus 0.8%, P = .053). The combined stroke/death rate was higher in octogenarians (3.1% versus 1.5%, P = .041).

These results of older patients are not so different from those observed in the RCTs of younger patients, implying that even octogenarians benefited from CEA. At least, age *per se* should not be considered a high-risk criterion for CEA.

CEA for Restenosis

The prospective ACAS follow-up data was interrogated to determine the rate of recurrent carotid stenosis (60% or more) based up angiogram-validated Doppler data in asymptomatic carotid stenosis (39). Early restenosis (3-18 months after CEA) was found in 7.6% to 11.4%; and late restenosis (18-60 months after CEA) occurred in 1.9% to 4.9%. Patch angioplasty closure showed a statistically significant effect on recurrent stenosis. Other previously reported factors related to recurrent carotid stenosis, including continued smoking, female sex, and hyperlipidemia, failed to show statistical significance. There was no correlation between late stroke and recurrent stenosis.

Carotid endarterectomy for restenosis is considered a technically demanding procedure compared with primary CEA. O'Hara et al reported the largest series of redo CEA for carotid restenosis (206 CEAs in 199 patients) (47). The 30-day stroke and death rates were 3.4% and 1.0%, respectively. Two early postoperative deaths (1.0%) , both from cardiac complication, occurred in patients who underwent redo CEAs combined with myocardial revascularization procedures. Therefore, there was no perioperative death for isolated redo CEA in this series. On the other hand, Herzter et al analyzed the stroke and mortality rates for 2228 consecutive CEAs (2046 patients), which incidentally contained a total of 153 reoperations for recurrent carotid stenosis (26). The perioperative stroke and mortality rates were 0.5% and 1.8% for all isolated CEAs, and 4.6% and 2.0% for carotid reoperations. The composite stroke and mortality rate for isolated CEA was significantly influenced by carotid reoperations (p = 0.024). Mozes summarized the results of 8 studies including symptomatic and asymptomatic cases, and reported the weighted average of perioperative stroke and death rates was 3.4% and 1.2%, respectively (41). These figures seem to be somewhat higher than the usual results from series of primary CEA.

Contralateral Carotid Occlusion

It has been suggested that the presence of contralateral carotid artery disease could further modify the effect of CEA. Subgroup analysis of NASCET data demonstrated that the perioperative rate of stroke and death is 14.3% if the contralateral artery is occluded as compared to 4.0% and 5.1% if the contralateral artery is still patent with severe and mild-to-moderate stenosis, respectively (21). Despite higher perioperative morbidity in the presence of an occluded contralateral artery, the outlook at 2-year for patients who had endarterectomy performed on the symptomatic, severely stenosed (70-99%) ipsilateral carotid artery was considerably better than for medically treated patients (22.1% versus 69.4%). On the other hand, post-hoc analysis of ACAS data showed that the perioperative (30-day) event rate (2.3% versus 2.2%) and 5-year ipsilateral stroke rate (5.5% versus 5.0%) were equivalent in patients with and without contralateral occlusion in the surgical arm (6). However, among those with a contralateral occlusion, the estimate of the 5-year event rate was 3.5% for medical management and 5.5% for surgical management, for a 2.0% increase in risk associated with surgical management. The Ontario CEA Registry included 533 patients with contralateral carotid occlusion and reported that contralateral carotid occlusion was a significant independent predictor for 30-day death or stroke rate.(8.8%, OR, 1.72 [6.0% in all patients]) (64). Comprehensive reviews on CEA for patients with contralateral carotid occlusion have been recently published (41, 53). The weighted average risk of stroke and death after CEA in 1038 patients with contralateral occlusion in nine studies was 2.7% and 1.0%, respectively (41). In 6793 patients without contralateral occlusion the perioperative stroke and death rate was 2.0% and 0.7%, respectively. However, the differences were not statistically significant. These results suggest that CEA with contralateral carotid occlusion may be related to slightly increased perioperative risk.

Carotid Stenosis after Cervical Radiation

In a comparative cross-sectional study, late carotid artery stenosis (>70% or more) was detected in 28 (11.7%) of 240 patients who had received external irradiation to the head and neck area (11). Brown et al reported a historical prospective cohort study of carotid artery stenosis in 44 head-and-neck cancer survivors who received unilateral neck radiotherapy (9). The incidence of significant carotid stenosis (8 of 44 [18%]) in the irradiated neck was higher than that in the contralateral unirradiated neck (3 of 44 [7%]), although this difference was not statistically significant.

Surgical dissection in a previously radiated field is technically challenging, and leads to risk for tissue necrosis, infection, and ulceration. Only small series of CEA for stenosis after neck irradiation are available. Mozes summarized the results of 5 studies, and reported the weighted average of perioperative stroke and mortality rate was 3.0% and 1.0%, respectively (41). However, the outcome variables were distributed over a wide range from 0% to 10%. In review of 776 CEAs at Mayo clinic, cervical radiation therapy was one of the four factors associated with significantly increased stroke risk although there were only 6 patients who had received the irradiation (29). More recent two studies including 11 and 17 CEAs reported

no perioperative stroke and death (10, 36). At this time the available data are insufficient to declare that cervical radiation therapy is related to increased perioperative risk.

Local Versus General Anesthesia

Local anesthesia for CEA may offer advantages over general anesthesia (52). Patients operated on under local anesthesia seem to have several advantages, such as better perioperative hemodynamic stability, simple and direct evaluation of the patient's neurological status during surgery, reduced requirements of intraoperative shunts, reduced duration of intervention and hospital stay, cost effectiveness, substantial decrease in complications.

However, local anesthesia may be associated with several problems (52). The CEA under local anesthesia may be a technically demanding procedure compared with CEA under general anesthesia. Patients may experience undue stress and pain during the CEA, which may result in an increased risk of myocardial infarction. Some surgeons may find CEA under local anesthesia more stressful.

On the other hand, general anesthesia is also suitable for non cooperating patients and eliminates anxiety and discomfort, thus creating optimal operative conditions for the surgeon, and allows increase of cerebral flow and perfusion, by modulating CO2 and arterial pressure.

Rerkasem et al summarized the results of seven RCTs (554 operations) that compared local and general anesthesia for CEA (52). All deaths within 30 days of operation were 1/280 (0.36%) and 6/274 (2.2%), all strokes and deaths within 30 days 7/280 (2.5%) and 11/274 (4.0%) in local and general anesthesia group, respectively. Myocardial infarction (MI) within 30 days was 4/280 (1.4%) and 5/274 (1.8%) in local and general anesthesia group, respectively. There was no significant difference between the two groups.

In addition, Rerkasem et al also summarized 41 non-randomized trials (25622 operations). All deaths within 30 days of operation were 79/8202 (0.96%) and 116/9501 (1.2%), respectively. The result was statistically significant at the 5% level ($p = 0.04$) with a fixed effect model, but not significant with a random effects model. All strokes and deaths within 30 days were 99/4122 (2.4%) and 505/9425 (5.4%) in local and general anesthesia group, respectively. Significantly fewer patients in the local anesthesia group suffered a stroke or died compared with the general anesthesia group. Myocardial infarctions (MIs) within 30 days were 84/7572 (1.1%) and 239/7201 (3.3%) in local and general anesthesia group, respectively. CEA under local anesthesia was associated with a significantly lower risk of MI. Latest non-randomized studies also demonstrated that local anesthesia was associated with a reduction in intraoperative shunting and perioperative stroke, and the duration of hospital stay (38).

These results of non-randomized studies seem to suggest superiority of local anesthesia over general anesthesia for CEA. However, most of the non-randomized studies were retrospective and some included non-consecutive cases. Therefore, some bias may have been introduced. For example, there appeared to be more patients in the local anesthesia group who had CEA for asymptomatic carotid stenos, suggesting that these patients may indeed

have been at lower risk of poor outcome (52). In conclusion, there is no reliable evidence to guide the choice of whether to use local or general anesthesia for CEA.

Shunt

Some perioperative strokes of CEA may result from the temporary interruption of blood flow that occurs while the carotid artery is clamped. The duration of interrupted blood flow to the brain can be minimized by the use of shunt as a temporary bypass. Although some surgeons depend on routine shunting, others prefer to use shunts selectively or avoid them altogether. Potential disadvantages of shunting include complications such as air and atherothrombotic embolization, carotid artery dissection, and an increased technical difficulty of the operation.

Bond et al summarized the results of two trials (590 patients) compared routine shunting with no shunting (7). The 30-day death rate was 1.1% and 2.4%, 30-day stroke rate 4.0% and 5.2% in shunted and nonshunted patients, respectively No significant differences were seen in any of the recorded outcomes for shunted versus nonshunted patients. They stated that there is still insufficient evidence from randomized controlled trials to support or refute the use of routine or selective shunting during carotid endarterectomy.

Selective use of shunt requires a highly specific and sensitive method of monitoring for cerebral ischemia. However, there is little evidence to support the use of one form of monitoring over another for such purpose. The electroencephalogram (EEG) and somatosensory evoked potentials (SEP) have been mainly used for this purpose as the standard. SEP provides less widespread cortical assessment when compared to multichannel EEG. However, SEP provide integrity of sensory pathway including brain-stem and sub-cortical white matter while EEG does not. A progressive cerebral blood flow (CBF) reduction gives rise to EEG attenuation (i.e. decrease in amplitude) and slowing (decrease in alpha (8-13 Hz) and beta waves (>13Hz), increase in theta (5-7 Hz) and delta (0.5-4 Hz)) waves. Brain hypoperfusion provokes an amplitude decrease or even the disappearance of N20 of SEP. In most studies, significant values are a more than 50% decrease in N20 amplitude and a central conduction time increase of more than 1 ms (18).

Florence et al summarized the results of six studies in which both EEG and SEP were applied to the same patient during CEA (18). For detection of cerebral ischemia during carotid clamping, the mean SEP sensitivity (0.57) appeared higher than that of EEG (0.20) while mean EEG and SEP specificities were similar (0.92 and 0.92 respectively). When the data were pooled, SEP were more sensitive and specific (0.60 and 0.97, respectively) than EEG (0.20 and 0.95, respectively). Odds ratios of SEP and EEG are 48.26 and 4.98 suggesting the superiority of SEP.

Our own data demonstrated similar results. Between 1999 and 2005, 108 consecutive patients underwent CEA with routine shunt under EEG monitoring. Three patients (2.8%) experienced transient global ischemia after CEA despite of the use of shunt. Postoperative diffusion MRI demonstrated no new ischemic lesion. All of the three recovered completely within 24 hours. Two of the three were monitored simultaneously with both of SEP and EEG during surgery. The SEP disappeared shortly after carotid clamping and partially recovered

after carotid declamping while EEG demonstrated no attenuation or slowing during surgery (Figure 1).

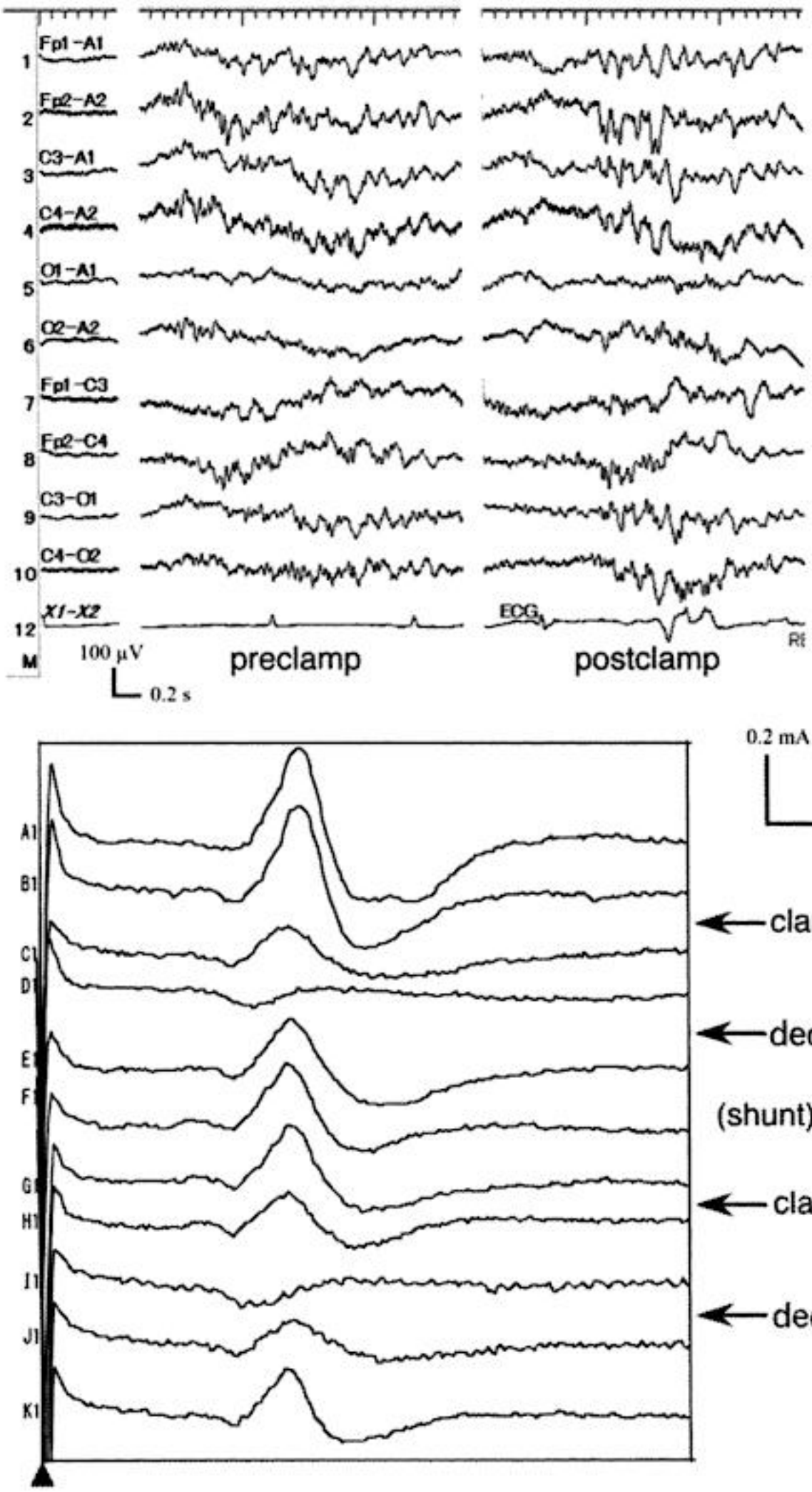

Figure 1. Simultaneous monitoring of patients by electroencephalogram (EEG) and somatosensory evoked potentials (SEP) of a patient with right carotid stenosis during carotid endarterectomy (CEA). Top, The EEG demonstrated no attenuation or slowing after internal carotid artery (ICA) clamping. Bottom, Temporal change of SEP during surgery. The SEP disappeared shortly after ICA clamping and recovered partially after ICA declamping. This patient experienced transient left hemiparesis after CEA. She completely recovered 10 hours after surgery.

EEG monitoring depends on the skill of the observer. On the other hand, SEP is relatively easy to evaluate. Digital EEG can provide more condensed data whose interpretation seems more readily accessible (18).

Hyperperfusion Syndrome

Hyperperfusion syndrome is a rare but disastrous complication after CEA and CAS. The classic triad includes unilateral headache, seizures, and intracerebral hemorrhage (50). The prognosis of intracerebral hemorrhage after CEA is miserable, with mortality rates of 36% to 63%, and survivors have significant morbidity (28). Most studies report the incidence of hyperperfusion syndrome after CEA between 0-3% (65). However, less florid manifestations of hyperperfusion are probably more common. Almost all reports provide evidence of hyperperfusion increasing more than 100% from baseline (Figure 2 and 4), although some patients can develop symptoms and signs with moderate increases in CBF (33). Persistence of hyperperfusion longer than a couple of days was reported to be associated with the development of hyperperfusion syndrome (Figure 2) (44). Most authors have reported the onset of hyperperfusion syndrome within several hours to several days after CEA (28, 44, 65).

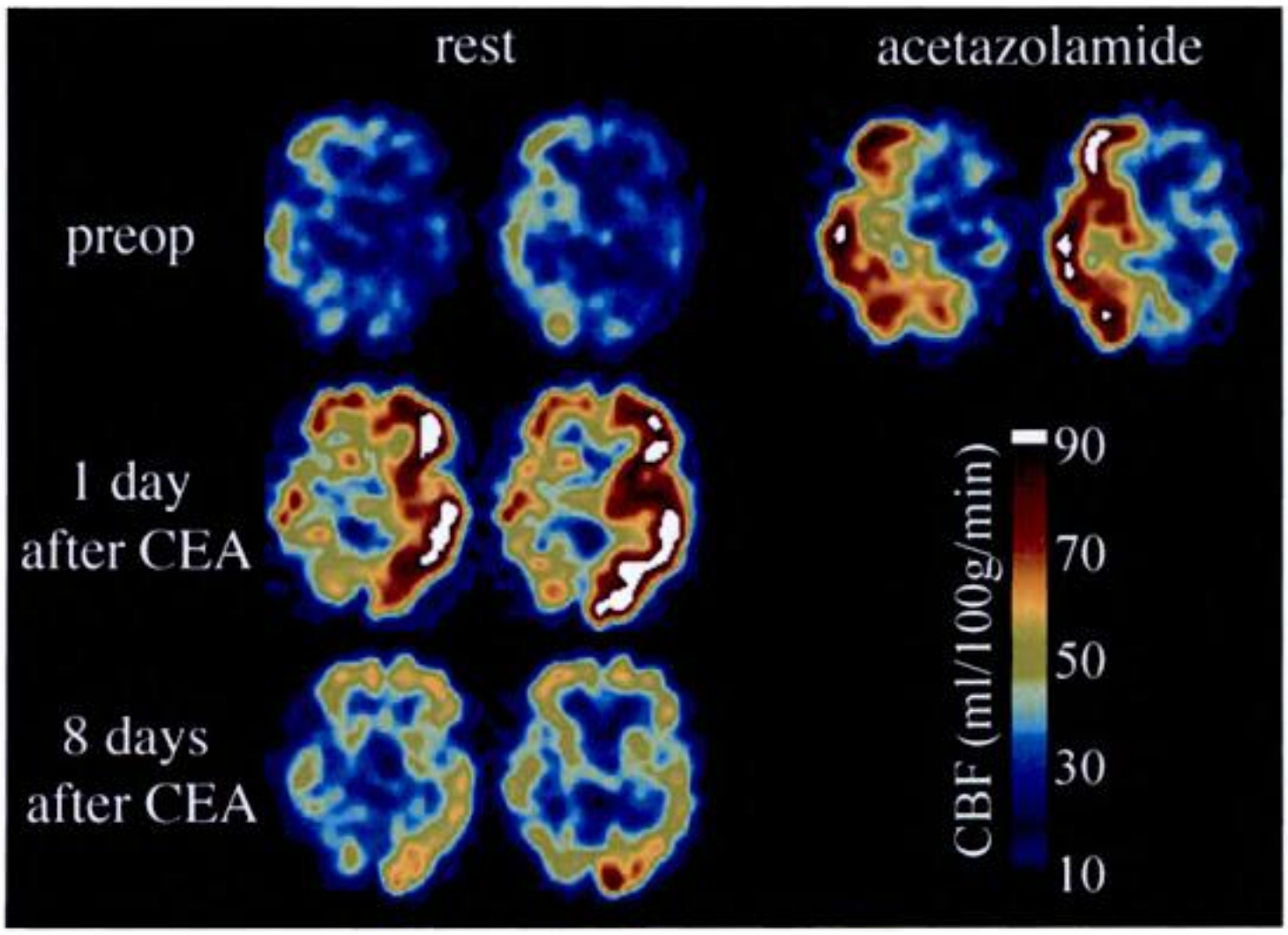

Figure 2. A case of hyperperfusion syndrome with severe left carotid stenosis after carotid endarterectomy. Top, preoperative SPECT. Severe hypoperfusion is seen in the left ICA territory on resting SPECT. Middle, SPECT on the first postoperative day clearly demonstrates hyperperfusion (>90 mL/min/100 gm, >100% increase of CBF) in the left ICA territory. Moderate CBF increase is also seen in the right ICA territory. Bottom, SPECT 8 days after carotid endarterectomy. Moderate CBF increase is still present in the left ICA territory. Rainbow displaying CBF from 10 to 90 mL/min/100 gm appears on the right.

As described in the previous part of this chapter, the perioperative stroke and death rates associated with CEA have significantly declined. For example, the mean 30-day mortality in Medicare beneficiaries in the United States relatively declined by 54% from 1991 (1.95%) to 2000 (0.89%) (59). This reduction may be attributed to a combination of experience and technical sophistication. With a reduction of technical error, the hyperperfusion syndrome has assumed a major role in the perioperative risk of CEA. Recent reviews reported that hyperperfusion syndrome caused 22-60% of perioperative strokes (3, 4, 13, 66).

Risk factors of this syndrome include long-standing hypertension, a high-grade stenosis, poor collateral blood flow, and contralateral carotid occlusion that often impair cerebral hemodynamic reserve (28). A rapid restoration of normal perfusion pressure after removal of a tight stenosis by CEA could cause a large increase of blood flow through the internal carotid artery (ICA) and hyperperfusion in a region of the brain that had been chronically ischemic with autoregulatory vasoparalysis. In other words, hyperperfusion after CEA may be equivalent to normal perfusion pressure breakthrough to describe the cerebral edema and hemorrhage that sometimes occur after the resection of a large and/or high-flow arteriovenous malformation (AVM) (61). Experimental cat model of AVM showed that the perfusion pressure breakthrough threshold in the chronically ischemic brain may not be reduced by the restoration of normal blood flow, but may be decreased by the addition of new ischemic insults or hypertension (57). These findings suggest cross clamping during CEA may further impair autoregulation. However, the duration of ICA clamping was not a significant independent predictor of hyperperfusion immediately after CEA (44). The same model also demonstrated that chronic cerebral ischemia caused increased capillary density and absent astrocytic foot processes in some of these vessels (58). Whether these changes also occur in humans with carotid stenosis remains to be seen, these anatomical configuration might make the capillaries prone to mechanical weakness and instability following the increase in perfusion pressure that occurs after CEA.

Hyperperfusion, which is classically defined as a CBF increase of ≥100%, was reported to be a significant risk factor for intracerebral hemorrhage (25, 50). Of those with CBF increase of ≥100%, intracerebral hemorrhage developed in 3.3%. In contrast, only 0.24% of those with CBF increase <100% developed intracerebral hemorrhage. Taken together, the risk of intracerebral hemorrhage in patients with hyperperfusion was 10 times that of patients without hyperperfusion. Therefore, prediction and detection of hyperperfusion after CEA is important in identifying patients at risk of intracerebral hemorrhage after CEA. Previous studies had suggested that patients with preoperative hemodynamic failure run a definite risk for hyperperfusion syndrome (28, 44, 50). Therefore, the preoperative assessment of cerebral hemodynamic reserve is important in predicting this rare but potentially devastating complication.

Prediction and Detection of Hyperperfusion Syndrome

Single-photon emission computed tomography (SPECT) can directly measure CBF baseline and hemodynamic status (after acetazolamide challenge), which is an ideal modality for prediction and detection of hyperperfusion (12, 27, 34). The cerebral vasoreactivity

(CVR) to CO2 or acetazolamide has been proposed as a test for cerebral hemodynamic reserve (12, 34). Acetazolamide is a carbonic anhydrase inhibitor that causes a disequilibrium of the CO2 buffer system. The vasodilating effect of acetazolamide given intravenously has been found at least as effective as inhalation of 5% CO2 (27). Administration of the drug induces a rapid and marked increase in CBF, ranging 20 to 80% (12, 27, 34). The CVR was defined as percent increase of CBF from baseline after acetazolamide challenge. Our SPECT study demonstrated that a significant CBF increase on the first postoperative day was seen only in the reduced CVR group but not in the normal CVR group (Figure 3) (28). A significant association of severely impaired hemodynamic status with hyperperfusion on the first postoperative day was observed. No patient in normal CVR group demonstrated postoperative hyperperfusion. The similar results were obtained in other studies (44). Ipsilateral CBF significantly decreased 1 month after CEA compared with the values on the first postoperative day in the reduced CVR group, returning to the normal range, but the CBF did not significantly change in the normal CVR group (Figure 3). No significant difference was observed between preoperative CBF and CBF 1 month after CEA in both groups (Figure 3). In some patients, however, preoperative hypoperfusion was remarkably improved. More recently, we used a statistical mapping method to reduce interobserver variability in the evaluation of SPECT studies and demonstrated that asymmetric reduction of baseline CBF and/or CVR reduction had a high diagnostic value to identify patients at risk for hyperperfusion after CEA. (Figure 4) (29-31).

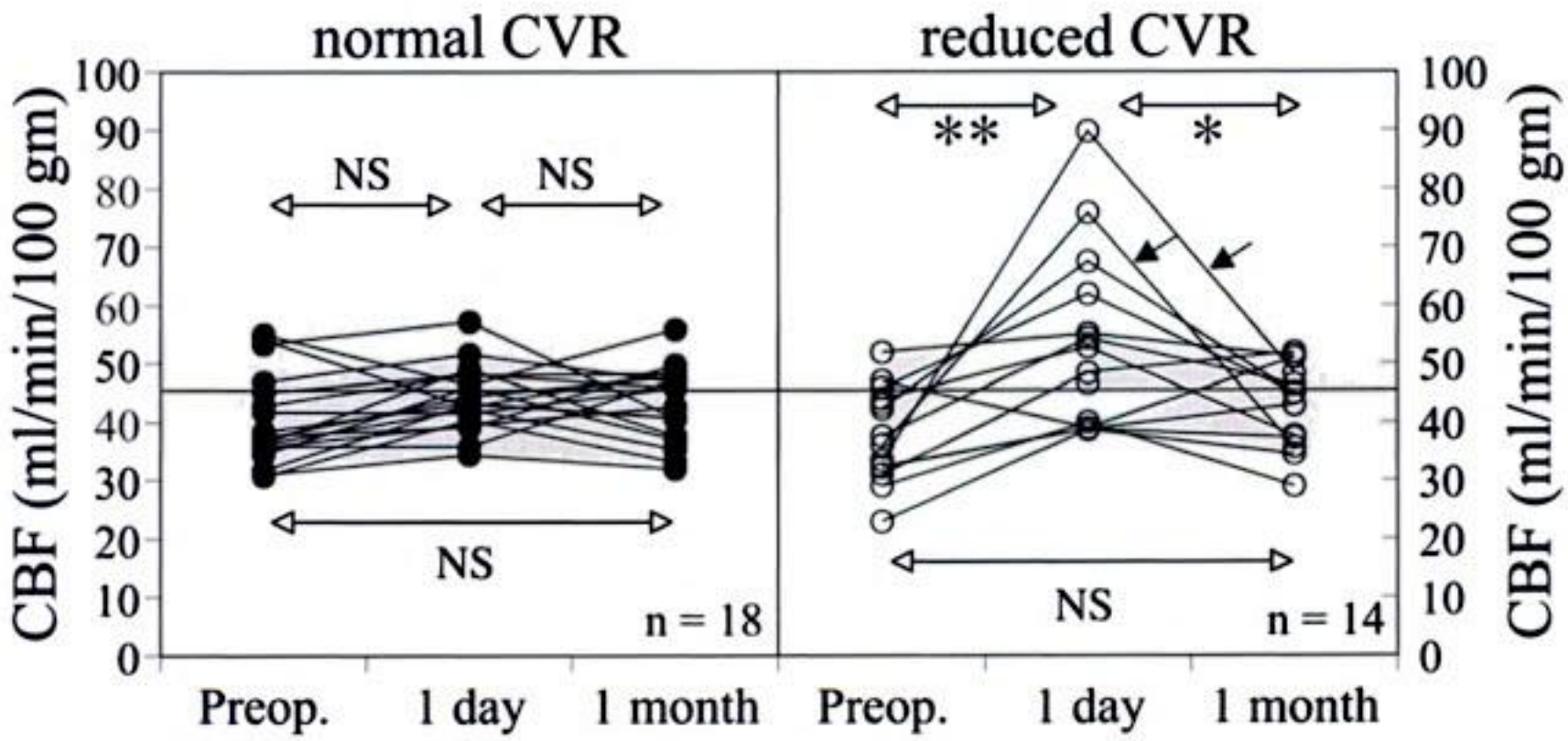

Figure 3. Preoperative and postoperative CBF on the side ipsilateral to carotid endarterectomy measured by SPECT with N-isopropyl-p-[123I]iodoamphetamine (IMP) combined with a modification of arterial input sampling. Left, Normal CVR group (CVR ≥12%). Right, Reduced CVR group (CVR <12%). Shaded areas are mean±2 standard deviations of 10 normal controls in our hospital. Black arrows indicate 2 patients who demonstrated ipsilateral CBF increase of ≥100% on the first postoperative day. Note CBF significantly changes after CEA in reduced CVR group, but not in normal CVR group. **,*Significant difference between each time point, *: $p = 0.025$, **: $p = 0.003$. NS: not significant. CVR: cerebral vasoreactivity.

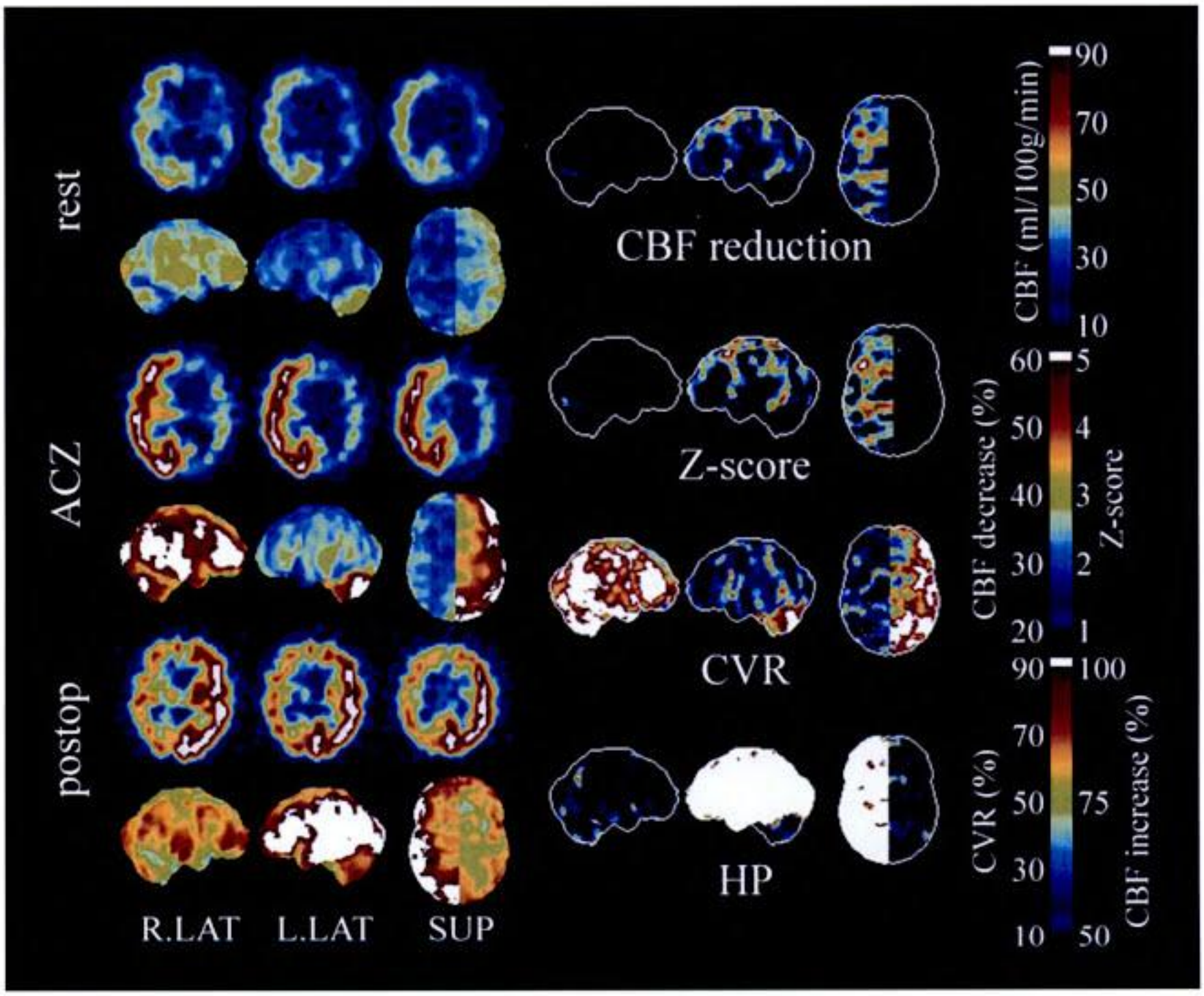

Figure 4. Image analysis of a patient with left carotid stenosis. Left, original SPECT transaxial slices (upper) and cortical surface maps of three-dimensional stereotactic surface projection (3D-SSP) on a pixel-by-pixel basis (lower). Preoperative resting SPECT (rest) demonstrates severe hypoperfusion in the left ICA territory, and acetazolamide (ACZ) challenge SPECT shows low CBF response to acetazolamide in the same territory. Postoperative resting SPECT (postop) demonstrates hyperperfusion in the same territory. Right lateral (R. LAT), left lateral (L. LAT), and superior (SUP) views. Right, cortical surface maps of 3D-SSP. CBF reduction, percent reduction of CBF is displayed on a pixel-by-pixel basis. Z-score, normalized activity of each patient was compared with the reference control database by means of a Z score. A Z score was calculated for each surface pixel: Z score = ([normal mean]—[individual mean])/(normal standard deviation). A region with reduced CBF (z-score >2) is expressed as a colored region and a region with normal CBF (z-score ≤2) as a black region. CVR, a region with reduced CVR is easily recognized as black pixels. HP, surface maps of CBF percent increase 1 day after CEA. Hyperperfusion is easily recognized as white pixels. CVR: cerebral vasoreactivity.

Internal carotid artery (ICA) blood flow increase after reconstruction measured by electromagnetic flowmeter during CEA significantly correlated with the ipsilateral CBF increase on the first postoperative day in the reduced CVR group but not in the normal CVR group (Figure 5) (28). This result also suggests that an extremely large increase of ICA flow after reconstruction occurs only in patients with severely impaired cerebral autoregulation. The 95% confidence interval associated with a predicted mean ICA flow increase for 100% CBF increase on the first postoperative day is 183 to 296 mL/min.

The threshold of ICA flow increase for hyperperfusion was estimated to be about 180 mL/min in the reduced CVR group (Figure 5). During surgery, therefore, an ICA flow increase after reconstruction may be a good indicator of hyperperfusion after CEA.

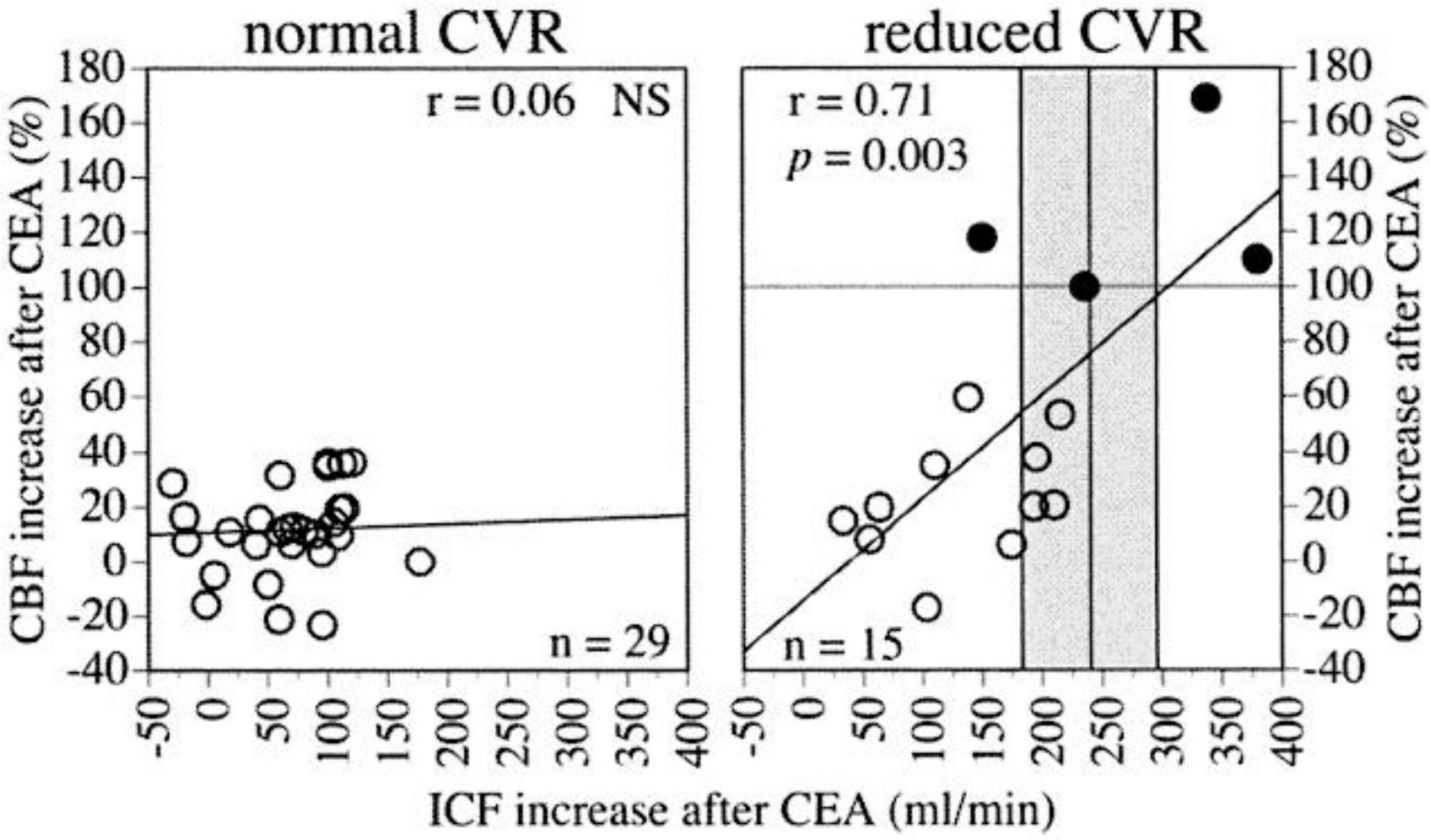

Figure 5. Correlation between internal carotid artery blood flow (ICF) and CBF increase after carotid endarterectomy (CEA). Left, No significant linear correlation was observed between ICF increase after reconstruction and ipsilateral CBF increase on the first postoperative day as a percentage of the preoperative CBF in the normal CVR group. Right, A significant linear correlation was observed between ICA flow increase after CEA and ipsilateral CBF increase on the first postoperative day as a percentage of the preoperative CBF in the reduced CVR group (correlation coefficient r=0.71, P = 0.003). Shaded area indicates 183-296 mL/min increase of ICA flow, which is 95% confidence interval for CBF increase of 100% as definition of hyperperfusion. Black circles indicate patients with hyperperfusion.

Transcranial doppler (TCD) can provide direct and real-time monitoring on middle cerebral artery (MCA) flow indicative of preoperative hypoperfusion, cerebrovascular reactivity, postoperative hyperperfusion, and emboli (14, 32, 65). An increase of MCA peak velocity or pulsatile index of ≥100% after declamping of the ICA was reported to be associated with intracerebral hemorrhage after CEA (32). This TCD criteria for hyperperfusion seems to be analogous to hyperperfusion criteria in CBF measurement. Furthermore, repeated observations are more practical with TCD than SPECT. As noted previously, persistence of hyperperfusion was reported to be associated with the development of hyperperfusion syndrome (Figure 2) (44). When cerebral hyperperfusion persists longer, repeated TCD measurements are made until cerebral hyperperfusion and symptoms have disappeared. However, symmetrically elevated velocities in both MCA were seen in a patient with ipsilateral hyperperfusion identified on SPECT (5). In addition, TCD monitoring is not

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Chapter 7

Joint Effects of Hyperlipemia with Hypertension and COCs. Use on the Risk of Stroke in Chinese Women

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Abstract

Combined oral contraceptives (COCs) have been popular for their effectiveness, convenience and reversibility since 1960s. There has however been increasing awareness of the risk of cardiovascular diseases (stroke, myocardial infarction and venous thromboembolism). Recent research has shown that there was an association between COCs exposure and stroke in women. The pathogenesis mechanism of stroke is extremely complicated, and it is determined and affected by multiple factors.

Purpose

Clarify the joint effects of low-dose combined oral contraceptives (COCs) and hyperlipemia with hypertension on the risk of stroke in Chinese women; initially explore

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a possible pathogenesis mechanism of the effects of influencing factors on the risk of stroke in order to decrease adverse reactions to COCs.

Methods

The case-control study based on the population of 25 towns in surveillance regions from July 1, 2000 to June 30, 2004, the stroke index cases (157) were living and married women who were born after June 1932 and had stroke for the first time. Married hospitalized women with other diseases or neighborhood but cardiovascular diseases were selected as controls (267) at the same period as cases with age no more or less than 3 years compared with the cases.

Results

1. The mean systolic blood pressure (MSBP 162.48±26.21mmHg) of stroke group was significantly higher than that of control subjects by 33 mmHg ($P<0.01$), and the mean diastolic blood pressure (MDBP 95.28±15.05mmHg) of stroke group was significantly higher than that of control subjects by 16 mmHg ($P<0.01$).
2. Serum levels of TC, TG, APOB and Lpa of the cases were significantly higher than those of the controls, but the level of HDL-C of the cases was significantly lower than that of the controls. For hemorrhagic stroke cases, the levels of TC and APOB were lower than those of the controls, while for ischaemic stroke cases, the levels of TC, TG, APOB and Lpa were all lower than those of the controls.
3. Stratified analyses showed evidence of joint effects of hyperlipemia with hypertension and COCs use on the risk stroke.
4. Logistic regression analyses showed that hypertension was similarly significant risk factors for hemorrhagic stroke and ischaemic stroke, COCs exposure was significant risk factor for hemorrhagic stroke, hyperlipemia was significant risk factor for ischaemic stroke.
5. Logistic regression analyses of joint effects of COCs exposure and both hypertension and hyperlipemia showed that the joint effects of COCs use and hypertension had obviously effects on the risk of total stroke, the joint effects of hypertension and hyperlipemia was similar to effects joint effects of COCs use and hyperlipemia, had slight effects on the risk of total stroke, the joint effects of COCs use with hypertension and hyperlipemia had striking effects on the risk of total stroke, especially for hemorrhagic stroke.

Conclusions

It is clear that hypertension, hyperlipemia and COCs use were significant risk factors for stroke, and that the joint effects of COCs exposure and both hypertension and hyperlipemia significantly increased the risk of all stroke, especially for hemorrhagic stroke.

Keywords: *combined oral contraceptives, stroke, case control study, hypertension, hyperlipemia.*

Introduction

Combined oral contraceptives (COCs) have been popular for their effectiveness, convenience and reversibility since the 1960s. There has however been increasing awareness

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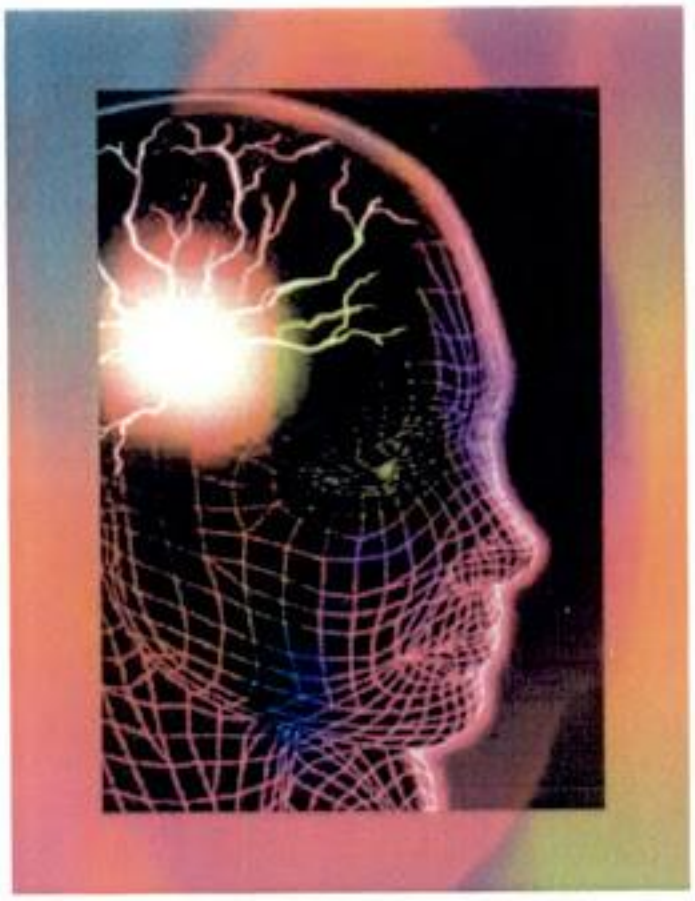

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