

# Extracranial-intracranial bypass surgery in cerebrovascular diseases

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### ABSTRACT

Since the report from the International Study on extracranial-intracranial bypass was presented in 1985, an abrupt stop to almost all bypass surgery was introduced. The clear goals of the bypass study to reduce repeated strokes based on extracranial-intracranial bypass could not be documented. This review emphasizes the drawbacks of this previous study and why its conclusions were too sweeping, including statements that the study could not validate. The present status on cerebral hemodynamics and possible augmentations of reduced cerebral vascular reserve using extracranial-intracranial bypass are given. It is concluded that in hemodynamic proven cases extracranial-intracranial bypass may definitely benefit the patients. This group of patients, among all stroke victims in the International Study, could not be deducted due to the study design. The high frequency of repeated serious strokes occurring among patients with hemodynamic insufficiency and its prevention by bypass surgery is documented. The right operation was carried out among a large group of 'wrong' patients. The prevention of repeated strokes that an extracranial-intracranial bypass allows us today, indicates that this operative method should also be possibly applied in the Kingdom under well defined hemodynamic circumstances.

**Keywords:** Extracranial-intracranial bypass, stroke, hemodynamic insufficiency.

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The blood supply to the brain arrives through the arterial network, the carotid and vertebral arteries, which intracranially are supplied by a collateral system, the Circle of Willis.<sup>1</sup> Thomas Willis wrote in 1664 in *Cerebri Anatome: Cui Accessit Nervorum Descriptio et Usus*: "... there may be a manifold way for the blood to go into diverse regions of the brain that if by chance one or 2 should be stopped there might easily be found another passage instead of them".<sup>2</sup> To a number of neurosurgeons, it still seems of interest to seek and establish alternative routes for augmentation of blood flow to the brain-parenchyma under certain circumstances,<sup>3-5</sup> despite the negative conclusions of the often quoted International Extracranial-Intracranial (EC-IC) Bypass Study.<sup>6,7</sup> This is difficult to obtain as neurologists throughout the world adapted the conclusions of this study without major reservations.<sup>8</sup> This review emphasizes the state of

the art today and is addressed mainly to neurologists in the field of cerebrovascular diseases.

**Purpose of an EC-IC bypass and relevant pathophysiology.** An EC-IC bypass increases blood flow to part of the brain. Where in the brain, depends on where the bypass is placed.<sup>9,10</sup> We may use direct so called low flow-, high flow- and indirect bypasses. The bypasses used in the International Study<sup>6</sup> were of the low-flow type.<sup>6,7</sup> Focal ischemia of the brain is the result of insufficient flow effect, distal to a vessel stenosis or occlusion.<sup>11</sup> Mechanisms producing focal ischemia vary: cardiac embolism, artery to artery embolism, small artery thrombosis and hemodynamic insufficiency.<sup>12</sup> The pressure within a major feeding artery of the brain drops to approximately 50% if e.g. the internal carotid artery (ICA) or middle cerebral artery (MCA) is ligated.<sup>13</sup> As these vessels have a passive role in autoregulation, a bypass adding blood volume and

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pressure to a point distal to the occlusion will increase pressure in the whole perfusion area of this artery.<sup>13</sup> Autoregulation takes place distally to these vessels, in the regulatory arterioles. An important factor for maintaining brain perfusion after the occlusion of a vessel, is the collateral circulation. The ophthalmic artery and other extracranial muscular arteries may serve as such. Most important is however, the Circle of Willis, the leptomeningeal, the transdural/transcerebral and the basal network that develops in Moyamoya disease.<sup>1,12</sup> Neuronal death occurs if distal cerebral blood flow (CBF) is below 10 ml/100g/min. Neurological deficits caused by moderate ischemia, e.g. flow between 10 and 23 ml/100g/min, can be reversed if flow is restored within hours.<sup>11</sup> The term "penumbra" or threshold of ionic failure, was originally introduced by Astrup and Symon<sup>14</sup> and indicates a state where neurons are functioning on a threshold between life and death. Only if CBF falls below 18-23 ml/100g/min for a prolonged period, or the distal blood pressure is below 30 mmHg, will an irreversible ischemic penumbra result.<sup>14</sup> The penumbra is dynamic, with a tendency to decrease in size over time. Despite non-functioning cortex, there is no major destruction of neurons in the majority of areas.<sup>15</sup> Reduced CBF may be found without clinical symptomatology if neurons are able to increase oxygen extraction and autoregulate flow optimally.<sup>16-18</sup> Reduced cerebral perfusion may also be found in "partial infarction", where some, but not all neurons have died.<sup>15</sup> These patients may have normal computerized tomography (CT) scans.<sup>15</sup> The ischemic penumbra is therefore often divided in one group with preserved neurons and one with varying degrees of neuronal loss. Standard CBF measurements cannot be used to differentiate between these 2 situations.<sup>4</sup> If the cerebrovascular reserve capacity (CVRC) reaches its limit, cerebral metabolism is maintained by increasing the oxygen extraction reserve (OER) from blood, as shown in positron emission tomography (PET) studies.<sup>19</sup> Among patients with maximally dilated intracerebral arterioles, a drop in blood pressure due to exhausted CVRC, results in a corresponding drop in CBF.<sup>20</sup> In addition, increase in tissue acidosis, lowered oxygen supply, increase in metabolic demands or occlusion of an artery may increase the physiological demand.<sup>18</sup> Cerebrovascular reserve capacity can only be assessed by measuring the hemodynamic response to a physiological stress such as alterations in blood pressure. The complexity of brain physiology is emphasized by the fact that, when cerebral hemodynamics are maximally impaired, other systems such as the brain renin-angiotensin axis may create a compensatory cerebrovascular hypertension.<sup>21</sup> It is therefore mandatory to find ways to differentiate between these situations. This is a problem yet to be solved, although methods are improving. Clinical

evaluations cannot be used to determine which patients may benefit from EC-IC bypass.

**Hemodynamics - methods.** Single photon emission computerized tomography (SPECT) with acetazolamide (Diamox<sup>®</sup>) loading, using inhalation or intravenous route is the most reliable and commonly used technique to demonstrate the intracranial vasculature.<sup>9,18</sup> Positron emission tomography studies have confirmed the value of using hemodynamic testing as a tool for judging patients who might benefit from an EC/IC bypass.<sup>22</sup> For practical, clinical use, only the <sup>133</sup>Xenon SPECT, transcranial doppler (TCD) and Xe-CT studies with estimation of cerebrovascular reserve capacity (CVRC) are of use.<sup>4,9</sup>

**1) <sup>133</sup>Xenon SPECT.** Inhalation of radioactive Xenon is used to test brain hemodynamics in a qualitative and semiquantitative way.<sup>18,23</sup> Acetazolamide has a strong vasodilatory effect upon the cerebral vessels, comparable to CO<sub>2</sub> inhalation. In normally perfused regions, acetazolamide will induce a CBF increase of about 30%.<sup>24</sup> However, in regions with a reduced perfusion pressure, as is the case in the hemisphere ipsilateral to an ICA occlusion with poor collateral supply, only a modest CBF increase will be seen. In some cases, a focal decrease in CBF may even be induced if the vessels at rest are dilated maximally in order to preserve flow, thus creating a steal phenomenon. Therefore, in hemodynamic cases, a marked asymmetrical flow response is induced during the stress test. Evaluation of the CBF studies is carried out by calculating both the absolute flow values and the regional flow distribution. The Diamox Asymmetry Index (D) defined by Vorstrup<sup>25</sup> as: the interhemispheric side to side asymmetry index for a given region of interest (ROI). By calculating the degree of change in side-to-side asymmetry of a ROI after acetazolamide injection, 'D' the difference in percentage increase of CBF in the 2 hemispheres or ROI's can be expressed as the absolute side difference taken in percentages of the higher values.<sup>25</sup>

**2) Transcranial doppler.** Transcranial doppler (TCD) determination is simple and can be used to identify significant occlusive vascular disease.<sup>20,26-28</sup> Ten percent of patients do not have a sufficient bone window which therefore invalidates the method. Cerebrovascular reserve capacity is better demonstrated by SPECT, than by TCD techniques, according to Schmiedek.<sup>4</sup> By being available in most centres dealing with cerebrovascular disease, the simple TCD technique is suitable for routine use or patient screening.<sup>26,27</sup>

**3) Xe-CT.** Cold Xenon CBF measurements on a CT scanner are a reliable test of CBF in a both quantitative and semiquantitative way.<sup>18,29</sup> Recent investigations correlating this technique with PET proves that it can be used to detect lesions of reduced cerebral blood volume and increased oxygen extraction.<sup>30</sup>

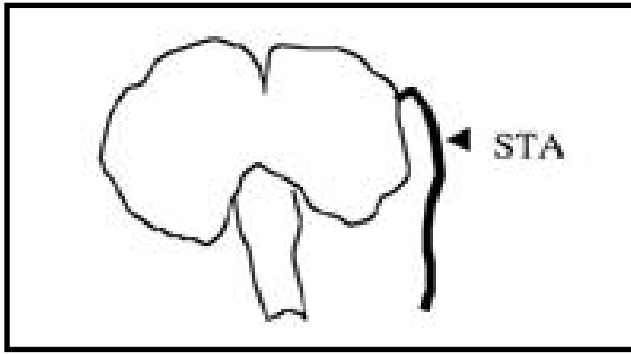


Figure 1 - Low-flow EC-IC bypass. STA - Superficial Temporal Artery.

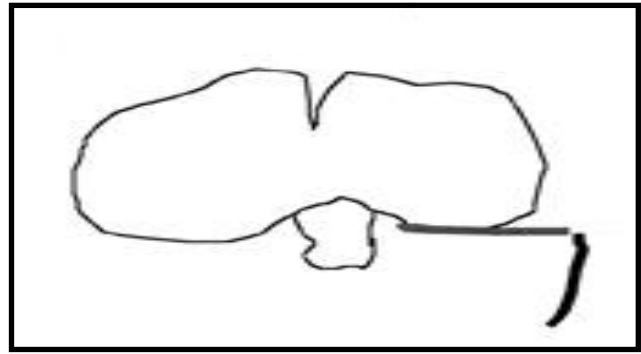


Figure 2 - Vein graft sutured to middle cerebral artery.

**Techniques of EC-IC bypass.** 1. A low-flow EC-IC bypass using the superficial temporal artery (STA) will deliver 25 to 80 ml of blood per minute depending on the size of the artery (Figure 1).<sup>9,31</sup> To increase flow delivered through the anastomosis, vein grafts have been inserted between the STA or the external carotid artery (ECA) and the cortical vessel, increasing flow to >100ml almost immediately.<sup>9,32</sup> The flow direction and placement of the bypass can easily be varied using grafts. The original EC/IC technique of Yasargil using the superficial temporal artery as a bypass, had an anastomotic patency rate of approximately 95%.<sup>9</sup> In this author's personal series of now over 270 cases, a similar patency rate was observed with a morbidity rate of 5%. The mortality rate was 2% and was related to cardiac acute myocardial infarct (AMI) in 3/4 cases.<sup>3,9</sup> 2. A "high flow bypass" where a donor vessel with a diameter of at least 2mm is connected with a relatively large, more distal recipient artery, may be more effective in revascularizing the brain in patients with hemodynamically caused ischemia (Figure 2).<sup>10,33,34</sup> Technically this procedure is more difficult, as it is carried out deep in the Sylvian fissure using MCA or ICA, added trauma through proximal, temporary occlusion and retraction of the brain may cause more complications.<sup>10,33,35</sup> Tulleken has, based on this, developed a technique first using a Neodymium<sup>35</sup> and thereafter an Eximer Laser<sup>10</sup> to create a side hole in the carotid artery. Performing the anastomosis he uses a vein graft sutured to the internal carotid artery wall. Passing the Eximer Contact Laser through the vein graft unto the adventitia of the ICA. The laser cuts a hole in the wall and the piece of wall is sucked out and the laser removed with closure of the side branch of the grafted vein. No temporary occlusion of the ICA is needed.<sup>10</sup> 3. Indirect methods are mostly used in treating Moyamoya disease.<sup>36</sup> Here galea, periosteum and muscle are used to create numerous small cortical neanastomosis. This is thus definitely a low flow method but can be used to cover larger areas of the brain surface. An alternative method is using free omental grafts sutured to the

superficial temporal artery and vein resulting in development of neanastomosis over the next 6 months.<sup>37</sup>

**How to select patients for EC-IC bypass?** Is reduced CVR closely related with clinical symptomatology? The answer is No! Is a neuroimaging study demonstrating arterial stenoses or occlusion of brain arteries enough? The answer is No! We usually think of symptoms of arteriosclerotic disease in the brain as transitory cerebral ischemic events (TCI), amaurosis fugax, bruits from the carotid arteries and stroke. Between 25 and 50% of patients with a large vessel occlusive or stenotic stroke will thus have had a prior TCI. Transitory cerebral ischemic events may be due to either emboli deriving mainly from the extracranial carotid arteries, or to hemodynamic deficiency.<sup>38</sup> Transitory cerebral ischemic events and their influence on symptomatology are still not thoroughly understood. Thrombotic strokes are by far the most common.<sup>39,40</sup> Embolic stroke may come from ulcerative plaques of the carotid arteries and seldomly form mural thrombi in the heart/heart valves. According to Caplan,<sup>12</sup> the use of the clinical parameters such as TCI, RIND, stroke in evolution and stroke, are not sufficient for clinical classification, as so many different vascular pathologies produce the same symptomatology. Schmiedek has discussed a series of clinical criteria for evaluating patients.<sup>4</sup> Also here, multiple factors are involved and selection criteria is not purely "clinical". In order to assess a carotid artery disease population Sundt<sup>41</sup> focused on risk factors in a patient population, an important factor in a randomized study. Thus it is evident that there are no optimal clinical definitions or grading as to who should undergo EC-IC bypass surgery. In cases of ICA occlusion, reverse flow through the ophthalmic artery is often found and ischemia of the retina may be the cause of amaurosis fugax. Flow through the ECA and ICA before and after EC-IC bypass was estimated by Jaksche.<sup>42</sup> It was concluded, that if a retrograde filling of the ophthalmic artery was found,

**Table 1** - International Bypass Study - results.

Outcome	Groups		
	MEDICAL	SURGICAL	TOTAL
Good	535	497	1.032
Bad	179	166	345
Total	714	663	1.377
BAD%	25%	25%	

the addition of a bypass would not benefit the patient, as the total intracranial flow would not change.<sup>42</sup> The ophthalmic flow would simply diminish to the same degree as the EC/IC bypass would increase flow. In contrast, if collateral flow was poor, a benefit of the EC-IC bypass on flow could be demonstrated.<sup>42</sup> The mathematical models of Hillen<sup>1</sup> and Chabrel<sup>43</sup> emphasizes this. With the aid of angiographic mapping, they developed computer models to determine flow in various areas and the influence of a EC-IC bypass on a specific area. If a standard EC-IC bypass is performed in all cases and if careful consideration to the above is not given, it is possible to perform the wrong operation on the right patient.<sup>9,35,44</sup> We have to accept, that at present, we have a limited ability to predict clinical outcome of cerebrovascular reconstructive procedures. This is partly due to complexity of symptomatology, variation in collateral circulation, pathophysiology and thereby producing major differences in patient populations. The only possible and clinical practical evaluation method today, is detection of a hemodynamically insufficient area of the brain by Diamox<sup>R</sup> loading SPECT or TCD investigations.<sup>24,25,27,45-47</sup> All other methods are considered experimental. This is of importance in the design of a randomized study, which cannot today be based on clinical symptomatology alone.<sup>5,48</sup>

**Own critique of the International EC-IC bypass study.** In 1985 almost all EC-IC bypass surgery stopped following the publication of the International EC-IC bypass study and an editorial.<sup>6,8</sup> The objective of the International EC-IC bypass study<sup>6,7</sup> was to determine whether EC-IC arterial anastomosis in the

carotid circulation could reduce, by 50% or more, the incidence of first or recurrent completed strokes among patients with certain forms of cerebrovascular disease, the latter being poorly described.<sup>31</sup> Demonstration of a stenosis or occlusion of a cerebral artery is not a reliable indicator of cerebral hemodynamics as there is an extensive intracranial collateral network.<sup>12</sup> For angiographic imaging, a full 4 vessel angiography is required to demonstrate new and absent collaterals as well as parent vessels in embolic areas or occlusions.<sup>9</sup> In the bypass study, this was not carried out. We have hypothesized, that a 10% subgroup in the International Study<sup>6,7</sup> could have benefitted from EC-IC bypass, but that the statistical design of the study could not prove it.<sup>44</sup> The official results of the International Study are presented in "table 2" from the study,<sup>6</sup> where "bad outcome" is major impairment or death and "good outcome" means no or minor impairment. Both the surgical and medical group had 25% bad outcome (Table 1). Let us assume that there is a 10% subgroup with a potential benefit, now called SELECT. This group does not, according to the EC-IC bypass trials,<sup>6</sup> differ in outcome from the other patients called REST (Table 2 can now be created). If good results were obtained in the surgical SELECT subgroup only, what would now, with constant marginal figures be the distribution in the surgical group, going from no effect from surgery, through some effect, to optimal effect of surgery? This is demonstrated in Table 3. As can be seen from Table 3, in a small SELECT subgroup of 10%, good results could be demonstrated and significantly differentiated from the medical group experiencing no effect. At what distribution of good and bad results in the SELECT subgroup would a comparison between surgical and medical subgroups yield significantly better results from surgery in the International EC/IC bypass study? This is shown comparing imaginary medical and surgical SELECT subgroups, keeping the results at 25% bad outcome in the medical SELECT subgroup and allowing the results in the surgical SELECT subgroups to become gradually better (Table 4). For optimal results in the SELECT subgroup, the price to be paid would be an increase from 25% to 28% in bad results for the REST group,

**Table 2** - International Bypass Study - with selected subgroup.

Outcome	Medical Group			Surgical Group		
	TOTAL	REST	SELECT	SELECT	REST	TOTAL
Good	535	481	54	50	447	497
Bad	179	161	18	17	149	166
Total	714	642	72	67	596	663
BAD%	25%	25%	25%	25%	25%	25%

**Table 3 -** Changes of bad outcome necessary for significant surgical result.

Outcome	SELECT subgroups			
	MEDICAL	SURGICAL	SURGICAL	SURGICAL
Good	54	50	58	67
Bad	18	17	9	0
Total	72	67	67	67
BAD%	25%	25%	13%	0%
Diff. Med/Surg*		NS	p<0.05	p<0.001

NS - non significant; \* - surgical 'select' groups - different figures.

a difference that would not have been found statistically. We concluded therefore, that a subgroup, ELECT, may be present in the International Study, not being statistically detectable.<sup>44</sup> These '10%' have later on, by TCD and SPECT studies, been shown to exist as hemodynamic CVR deficient areas of the brain.<sup>17,25</sup>

**Discussion.** Because of insufficient clinical and pathophysiological correlation, we know today that it is difficult (impossible) to prove a benefit from EC-IC bypass in patients who have transient ischemic attacks, mild strokes or transient monocular visual symptoms.<sup>31</sup> There is an interrelationship between embolic and hemodynamic factors in patients with combined stenotic and embolic carotid disease.<sup>17</sup> Strokes always occur on the side of the vascular lesion in patients with carotid siphon stenosis, MCA stenosis or MCA occlusion. Among the largest group of patients, those with an ICA occlusion, it was found that one third of the strokes during follow-up, occur on the contralateral side, emphasizing that embolic factors may not be the only cause of their symptoms.<sup>49,50</sup> An estimation of baseline CBF changes alone is not sufficient, as CBF is affected by embolic as well as hemodynamic ischemia.<sup>25,47</sup> As

both thromboembolic and hemodynamic factors contribute to the pathogenesis of cerebral ischemia, ICA occlusion as a primary inclusion criteria, reduces the likelihood of embolism being the major cause of symptomatology, the latter not being influenced by a standard EC-IC bypass.<sup>9</sup> Angiographic signs of Circle of Willis insufficiency with unilateral ICA occlusion, showing retrograde ophthalmic flow, seem to have a higher incidence of impaired CO<sub>2</sub> reactivity in the affected hemisphere.<sup>49,51,52</sup>

In a series of patients with increased risk, studied before and after EC/IC bypass, the vasodilatory stress test showed that, despite severe arteriosclerotic lesions, only 50% had an impaired collateral capacity.<sup>24,25,46,47</sup> In about 10% of the patients, an "intracerebral steal phenomenon" was observed suggesting a severely impaired regional perfusion pressure, with CBF around or below the lower limit of CBF increase in these patients.<sup>24,46</sup> In Denmark, Vorstrup and Lassen,<sup>46,47,53</sup> tested the reserve capacity of the penumbra using SPECT, and confirmed these findings. The spontaneous course of ICA occlusion is usually given with an annual stroke rate from 2-4% for asymptomatic cases and up to 5-9% for symptomatic patients.<sup>17,40,54-58</sup> So far, only a few studies<sup>17,56,58,59</sup> have been concerned with the spontaneous course of hemodynamically impaired ICA occlusions. Yonas,<sup>17</sup> Schmiedek<sup>4</sup> and Kleiser<sup>59</sup> were all able to show a higher risk of stroke in hemodynamically compromised subgroups with ICA occlusion. Yonas<sup>17</sup> found that 31% of his patients, that were followed for 2 years, developed an ipsilateral stroke. Of 68 patients followed for 24 months, 46 showed a flow variation of <5% with acetazolamide testing. These patients had a stroke rate of 4%. Among 22 patients with CBF that fell >5%, the stroke rate was significantly higher at 36% (p=0.0001). Strokes occurred only in vascular territory demonstrating a steal response.<sup>17</sup> In their series Kleiser and Widder<sup>59</sup> found patients, with exhausted CVR capacity ipsilateral to an occluded carotid artery, to have a significantly elevated rate of subsequent stroke. Out of 85 patients, almost 50%

**Table 4 -** Subgroups - hypothetical effect and influence on statistics in International Bypass Study. Why a surgical benefit could not be detected.

Outcome	Surgical Group			Surgical Group			Surgical Group		
	SELECT	REST	TOTAL	SELECT	REST	TOTAL	SELECT	REST	TOTAL
Good	50	447	497	58	439	398	67	430	497
Bad	17	149	166	9	157	166	0	166	166
Total	67	596	663	67	596	633	67	596	633
BAD%	25%	25%	25%	13%	26%	25%	25%	28%	25%
	No effect in			Some effect in			Optimal effect in		

developed strokes if CO<sub>2</sub> reactivity was exhausted, whereas those with normal function did not. The same results were found in a later series.<sup>58</sup> It is thus today possible to identify a small population of patients with cerebral ischemia caused by impairment of the CVR,<sup>14,23,60</sup> just as predicted by our analysis of the International study.<sup>44</sup>

**EC-IC operative results on hemodynamic cases.** Schmiedek<sup>4,27</sup> evaluated 28 patients defined using SPECT/Diamox<sup>R</sup>. Only patients with unilateral ICA occlusions (in order to avoid embolic sources) and recurrent episodes of cerebral ischemia were included. Normal CT or border-zone infarctions were accepted. Following EC-IC bypass, 2 died from AMI and one had a brain infarction with total major morbidity and mortality of 14%. With a mean follow-up of 3 years, no further brain ischemic events occurred. All arterial anastomosis were open on angiography. Resting CBF was unchanged, but augmented CVR increased.<sup>27</sup> In Japan, Yamashita<sup>61</sup> found that 13/18 patients with absent CVR improved after surgery. Vorstrup<sup>46</sup> showed that it is possible to restore both clinical and hemodynamic function with EC-IC bypass using the SPECT<sup>133</sup>Xenon inhalation technique as a clinical tool. Examinations were carried out pre and post-operatively and showed significant cortical flow improvement.<sup>46</sup> Among 22 patients with SPECT standard low flow areas, 18 showed no change with acetazolamide loading.<sup>46</sup> In a later series, 9 of 18 patients had a positive test before and only 2 of these after bypass.<sup>47</sup> All our later Danish patients showed more than 10% enhancement of "D" or slight or no increase of CBF.<sup>24</sup> In the ROI, the regional CBF auto-regulation test showed that during increase of MAP, inconsistent findings in both absolute flow values and "D" were observed. However during decrease of MAP, all patients showed a further CBF decrease in the low flow area (ROI), causing marked enhancement of the side-to-side asymmetry, e.g. increasing "D". Following EC-IC bypass, postoperative flow studies showed a modest CBF improvement of the baseline CBF, but a marked vasodilatory improvement during the acetazolamide test.<sup>24,25</sup> Powers<sup>62</sup> used PET to divide the hemodynamic cases into 2 groups, stage 1 and stage 2. Stage 1 cases have a restricted regional vasodilatory capacity as compared to normal tissue, whereas in stage 2, CBF is reduced below the lower limit of autoregulation due to decreased perfusion pressure. Vorstrup doubts that stage 1 patients can benefit from EC/IC bypass and that only stage 2 patients are of interest.<sup>24</sup> In Kuroda's study,<sup>63</sup> there were 4 groups based on CVR and CBF. Only the 2 groups with decreased CVR responded to EC-IC bypass in contrast to the groups with normal or decreased CBF.<sup>63</sup> These results are supported by Japanese studies on Moyamoya disease.<sup>36</sup> An increase in vasoreactivity or a decrease in OER in the postoperative phase after EC-IC bypass has not only been shown by our group but is verified in a slide of

papers.<sup>23,26,30,61,62,64-68</sup> We must today conclude that in order to identify patients with ICA occlusion who would benefit from surgery, we may only consider those with proven hemodynamic insufficiency/reduced CVR.<sup>18</sup> Clinically, these patients may have permanent or fluctuating minor neurological deficits or TIA.<sup>50</sup> This was not the case in the International Study which had over 60% of patients with fixed neurological deficits and proven infarction.<sup>6,31,35</sup> In the International study,<sup>6,7</sup> no hemodynamic parameters were included, and it was after publication, that several authors looked into the vasoreactivity problem.<sup>18</sup> By 1986, arguments were put forward that the negative results of the Bypass Study were due to inadequate selection of patients and inadequate statistics.<sup>5,9,31,44,69,70</sup> In a British editorial<sup>69</sup> it was stated "This conclusion cannot be supported from the trial, and the organizers are uncompromising in continuing to claim that their evidence shows that the operation must be laid to rest". Neither clinical evaluation nor a study of CBF alone can be used to selectively identify suitable patients for surgery, most important is the evaluation of CVRC.<sup>4,24</sup>

The limitations of clinical trials addressing surgical procedures on disease is evaluated by Bonchek.<sup>48</sup> The follow-up of these cases showed that the relative protective effect of the operation against death from stroke might conceivably distort the data toward a higher frequency of death from cardiac causes. Such an effect has been found by Wishnant<sup>71</sup> in the follow-up of patients who have undergone carotid endarterectomy. It should be recalled that the patient population for carotid artery operations includes 60% with coronary arteriosclerotic diseases, 54% with arterial hypertension, 50% with alcoholism and smoking habits and 39% with diabetes and obesity, e.g. a severely disabled population with very variable prognosis difficult to randomize.<sup>72</sup> Those patients who have the highest surgical risk because of frequency, severity and progressive character of the ischemic neurologic symptoms, are the patients who have the most to gain from the operation, as their course during follow-up approximates that of this selected group. In the International study,<sup>6</sup> the symptomatology may thus have been too minor<sup>31</sup> and the proposed goal erroneously chosen.<sup>9</sup> Among the general neurosurgical critique of the study,<sup>6</sup> extensive literature references have been given by Haase,<sup>9,44</sup> Day,<sup>31</sup> Dudley,<sup>69</sup> Warlow<sup>70</sup> and Sundt Jr.<sup>5,57</sup> and an editorial by Ausman with comments in Surgical Neurology.<sup>73</sup>

In conclusion, a single therapeutic modality, e.g. an EC-IC bypass, cannot be expected to be effective against widely different pathophysiological mechanisms. Symptoms of ischemia in the area of an occluded vessel are hemodynamic in origin in among 10-20%. Revascularization of such an ischemic area may be accomplished by surgery on the stenotic or occluded vessel or by bypass surgery. The

International Study focused on stroke or death and not quality of life. The subtle psychological changes we observed in our EC-IC bypass study<sup>74</sup> have never been investigated in a randomized study and quality of life was not part of the International Study.<sup>6</sup> Surgery should be reserved for those patients who have progression of symptoms or demonstrate an instability of neurologic (and neuropsychologic?) function after confirmation of internal carotid artery occlusion or siphon stenosis. In addition, visualization of collaterals, especially leptomeningeal vessels, impaired physiological collaterals (Diamox<sup>R</sup> SPECT/TCD) in the circle of Willis and positive imaging studies should be part of the clinical scenario. Demonstration of a hypoperfused area with a reduced CVRC for classification is today the most reliable, but not proven, method that identifies the patients to be treated.<sup>75</sup> However the final 'evidence based' answer to the question raised by Widder and Kornhuber:<sup>76</sup> Who benefits? Has yet to be answered.

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