Heart failure and cerebral ischemia

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Heart failure patients may have impaired cerebral autoregulation and regional cerebral blood flow abnormalities. Pre-disposition to thromboembolic complications occur because of dilated chambers and abnormal blood flow, abnormal vessel/chamber lining and abnormal blood particles in heart failure patients. Epidemiological and clinical studies document an increased rate of thromboembolic complications in heart failure. Well known/accepted indications of oral anticoagulation therapy to prevent thromboembolic events are co-existence of atrial fibrillation/flutter, intracardiac thrombi and a history of a thromboembolic event. Other than a co-existence of coronary artery disease and heart failure, antiplatelet agents should not be used in heart failure patients to prevent ischemic stroke. How and who to treat/prevent a thromboembolic event in patients with heart failure and sinus rhythm is a hot topic. Up to date, clinical studies of treatment with oral anticoagulant agents-mainly warfarin and recently rivaroxaban vs antiplatelet agents or placebo could not meet their primary outcome related with morbidity/mortality. In some of these studies, decreased rate of ischemic strokes were offset by increased major hemorrhage.

Keywords: heart failure, cerebral ischemia, stroke

Cerebrovascular coupling. Alterations in this mechanism can impair the brain vasculature to divert sufficient blood flow to active regions causing neural dysfunction (3, 4). Astrocytes are in direct contact with endothelial cells on the vascular smooth muscle and they can release vasodilatory substances as needed (5).

Cerebral Vasoreactivity
Cerebral vasoreactivity, another component of cerebrovascular control is the high sensitivity of cerebral vasculature to changes in arterial CO₂ and oxygen (O₂) levels. Hypercapnia causes vasodilation and an increase in flow while hypocapnia leads to vasoconstriction. So, vasodilatation in response to hypercapnia clears CO₂ off the brain circulation and conversely, vasoconstriction induced by hypocapnia attenuates the fall in brain pH (3).

Cerebral Autoregulation
Third mechanism, cerebral autoregulation helps to counteract fluctuations in systemic arterial pressure that can occur in daily activities. For instance, without effective cerebral autoregulation, sudden upright pos-
Heart failure as a risk factor for stroke: epidemiology

Heart failure (HF) is the second strongest independent risk factor for stroke after atrial fibrillation (AF) (8). Interestingly, a complex relation exists between HF and AF, for both, causing a tendency to other’s occurrence and a poorer clinical scenario, with an increased ischemic stroke risk when added to each other. An increased risk of venous thromboembolism, cardio-embolic stroke and sudden death occurs in approximately 30% of HF patients (9). Interestingly, in many studies reduced or preserved heart failure discrimination hasn’t been reported but it seems likely that more severely depressed reduced ejection fraction possesses further risk just like accompanying pulmonary hypertension and right heart failure (9). In a population based 30-year cohort study from Denmark incident HF patients were compared with age-sex-comorbidity matched general population controls. In this study, HF was associated with increased short and long term risk of all stroke subtypes suggesting that HF is a potent and persistent risk factor for stroke. During 31 days and 30 years risk of stroke were 1.5 to 2.1 fold for ischemic stroke, 1.4 to 1.8 fold for intracranial hemorrhage and 1.1 to 1.7 fold for subarachnoid hemorrhage (10). Importantly, in this study, authors take AF into consideration during follow-up and their analysis which makes the study more robust and valuable. Among patients presenting with stroke or peripheral thromboembolism the prevalence of HF, especially HF with reduced ejection fraction (HRrEF) or left ventricular systolic dysfunction (LVSD) is quite frequent. About 14% of patients with stroke have HF and approximately 20% of the stroke patients have some evidence LVSD (ejection fraction-EF < 50%) (11,12). Data on thromboembolic risk in HF from large epidemiological studies is somewhat problematic in terms of reporting/discriminating about HFrEF and HF with preserved ejection fraction. Another confounding point is reporting about concomitant AF, not all studies deal with this important issue (9).

In the Rotterdam Study, among 7546 patients aged >55 years who were followed for 10 years, risk of ischemic stroke was increased more than fivefold in the first month of diagnosis of HF but this risk of ischemic stroke attenuated over time and returned to normal after six months (13). This finding contrasts with the Danish study reporting consistent and persistent risk throughout 30 years of follow up (10). Patients with HF also have a high rate of stroke recurrence and mortality after stroke (14, 15). A well-known association exists between HF and venous thromboembolism (VTE), a two fold increase of VTE occurs with important outcomes for prognosis and death (16). Annual stroke rates of 1.1%–4.6% have been reported in HF trials, however many of these analysis included some patients with AF (9). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) reported the highest annual cerebrovascular event rate of % 4.6 among HF trials, but this trial included patients with severe LVSD and a high prevalence of concomitant AF (17). An analysis of Vasodilator Heart Failure Trials I-II (V-HeFT I and II) reported an incidence 2.7% and 2.1% of thromboembolic events per year in patients who were not using oral anticoagulation (18).

An analysis from the SCD-HeFT trial (Sudden Cardiac Death in Heart Failure Trial) of patients with NYHA class II and III without AF reported a 4 year incidence of thromboembolism (mostly strokes) 4%. Rate of subgroups were 2.6% for patients randomized to amiodarone, 3.2 5 for patients randomized to an internal cardioverter defibrillator (ICD), and 6% for patients randomized to placebo (19). Of note, decreasing left ventricular ejection fraction (LVEF) was a significant predictor of thromboembolism (HR: 0.82; 95% CI: 0.69–0.97 per 5% increase in EF).

In an analysis of data on warfarin use in SOLVD study (Studies of Left Ventricular Dysfunction), the authors found that warfarin use was independently associated with significant reduction in all-cause mortality (adjusted HR: 0.76, 95% CI: 0.65–0.89; p=0.0006) and in the risk of death or hospital admission for HF (HR: 0.82, 95% CI: 0.72–0.93, p=0.0002). Reduction in risk was not significantly influenced age, NYHA functional class or etiology of HF, EF, AF (20).

There are limited data on the rate of stroke in patients with HFpEF. Some data from post-hoc analysis of large clinical HFpEF studies document similar rates. For instance, the I-PRESERVE study (Irbesertan in Patiens with Heart Failure and Preserved Ejection Fraction) reported an annual rate of stroke as 0.8–0.9%, additionally 9% of all deaths were because of stroke (21). In the CHARM-Preserved study (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) rate of fatal and non-fatal stroke was unrelated to EF (EF <22% 1.2%, EE 23-32% 1.4%, EF 33-42 1.4%, EF 43-52 1.3%, and EF >52% 1.5%).

Pathophysiology

Increased rates of thrombotic complications in patients with HF has well known pathophysiological basis. Pre-
cipation to thrombogenesis is related with a combina-
tion of abnormal blood flow, abnormalities in the vessel 
wall and abnormalities in the blood constituents itself-
the Virchow’s triad (22).
Especially, in the setting of reduced LVEF, dilated 
chambers and a marked decrease in systolic function and a 
tendency for stasis of blood and thrombosis occurs in 
heart chambers. Blood flow abnormalities is common in 
dilated aneurysmatic heart chambers. In patients with 
large anterior myocardial infarctions- developing an 
apical aneurysm it is widely accepted to use antico-
agulant therapy for 3 months post myocardial infarction 
(MI) (9).
Another component of the Virchow triad is vessel wall. 
Around half to two thirds of patients with HFrEF have 
athero-thrombotic disease, underlying endothelial 
damage/dysfunction might precipate thromboembolic 
complications. In patients with HF impaired synthesis 
of endothelium derived nitric oxide may promote mono-
cyte and platelet adhesion to endothelium (23). Biologi-
cal markers of endothelial dysfunction and rheologic 
markers of thrombogenicity-, a hypercoagulable state 
indicators such as von Willebrand factor, thrombomod-
ulin, soluble e-selectin are found to be consistently ele-

cipated in patients with HF (24–26).
A high prevalence of anemia and iron deficiency is re-
ported in patients with HF that may additionally predis-
pose to thrombosis (27). Elevated levels of erythropoi-
etin which is commonly found in anemic – iron deficient 
patients, iron deficiency related reactive thrombocto-
ysis, increased platelet aggregation as a result of 
oxidative stress are the proposed components of iron 
deficient anemic patients’ predisposition to thromboem-

bolic events (9, 28).

Heart failure and stroke: clinical evaluation

It is quite common for the clinical cardiologist to be 
consulted by a neurologist for a stroke or transient is-
chemic attack (TIA) patient to evaluate the heart as a 
source of embolic phenomenon. In such a patient with 
non-valvular AF, the case is relatively easy- an appa-
rent cause of cardiac embolism. If the patient has no 
sign and symptoms of heart disease, no hypertension, 
and no diabetes mellitus and if ECG and chest x-ray are 
normal, possibility of a cardiac embolic event is very 
low. Especially, for a cryptogenic stroke case in a young 
to middle aged patient, performing an echocardiogra-
phy to evaluate for a patent foramen oval should be un-
taken as well as a Holter rhythm study to exclude 
paroxysmal atrial fibrillation or flutter. For an undeter-
mined etiology of stroke, it may be necessary to check for 
intrinsic hypercoagulability test.
In a systematic review of embolic stroke of undeter-
mined source, the authors concluded that so as to de-
fine an embolic stroke as “undetermined source”, there 
should be no major risk of cardioembolic source. In this 
review, major sources for cardioembolism are defined as 
follows; permanent or paroxysmal atrial fibrillation, 
sustained atrial flutter, intracardiac thrombus, prosthet-
ic cardiac valve, atrial myxoma or other cardiac tumors, 
mitral stenosis, recent myocardial infarction (<4 weeks), 
LVEF <30%, valvular vegetations or infective endocar-
ditis (29).
Especially, for cryptogenic embolism a high index of 
suspicion for PAF is prudent. Although we lack direct 
studies from HF populations, one systematic review 
demonstrated that PAF may be documented in 5% of 
ischemic stroke patients using prolonged ECG record-
ings (9, 30).

Imaging

In an transthoracic echocardiographic (TTE) study, in-
tracardiac thrombi would seem as echogenic, dense, 
heterogenous convex masses with clear margins. It 
can appear as sessile or pedunculated, locates close to 
thin dyskinetic ventricular segments or in the atrial ap-
pendage. Devices, tumors, vegetations, artefacts may 
resemble thrombi and a differential diagnosis should 
be made as needed. Intravenous agitated saline or 
transpulmonary contrast agents can help for diagnostic 
differentiation (31). So as to reduce cardioembolic risk 
anticoagulation is essential but age of the thrombus, 
echocardiographic appearance of an endothelized or 
mobility would affect treatment decisions and respon-
sible clinician should proceed accordingly.
In some certain circumstances, a transesophageal 
cho (TEE) study may help to have additional diagnost-
ic insights to TTE. TTE may be limited by suboptimal 
images (particularly in obese patients), restricted field 
for imaging cardiac apex and left atrial appendage. In 
a series of ischemic stroke patients the authors have 
performed TEE and the have explored thrombus in 25% 
of patients (32). Other than a visible thrombus, well known potential car-
dioembolic sources are; catheter leads, central lines, 
prosthetic valves, patent foramen ovale, spontaneous 
ecocontrast, thin mobile mitral strands, mitral steno-
sis, LV systolic and diastolic dysfunction and perhaps 
pulmonary vein ablation-isolation (33). In a study of is-
chemic stroke patients, patients with coronary artery 
disease (CAD), ECG evidence of ischemia or LVSD, 
large strokes, AF were more likely to have intracardiac 
thrombus on TOE (32). Thus, it is conceivable that clini-
cal clues of heart disease and LV dysfunction on TTE 
may help the clinician to proceed with a TOE depending 
on the individual circumstances.
In some patients, especially for morbid obese 
and those with poor echo image quality ultrafast computed 
tomography or magnetic resonance (MR) imaging may 
be helpful to detect intracardiac thrombus since they 
are less operator dependent and have high spatial and 
temporal resolution with better tissue characterization.
In one MR series, using gadolinium enhanced cardiac MR authors reported ventricular thrombi in 21% of patients with ischemic cardiomyopathy or prior MI. Of note, in less than half of patients with cardiac thrombus TTE was negative and in 5% of patients TTE gave false positive images (34). The difficulty with MR is that it’s not widely available and expertise and experience is important.

Heart failure – cerebral ischemia, prevention/treatment

In HF, a clinical condition that is a predisposing factor for thromboembolic events, antithrombotic treatment could be expected to prevent thromboembolic events. However, in order to have a net risk/benefit ratio of prevention of thromboembolism vs major bleeding-intracranial hemorrhage we need relevant reliable data. Interestingly, many of the HFrEF patients due to CAD would already be receiving an antiplatelet agent, mainly acetylsalicylic acid for prevention of atherothrombotic complications of CAD, which might also help to prevent stroke. Making issues even more complex, for instance, for registry studies is acute coronary syndromes and or implantation of drug eluting stents which would require dual antiplatelet therapy that might also help prevention of ischemic strokes. As reviewed above, unnoticed PAF may be the cause of ischemic stroke, a possibly confounding variable for clinical studies. We don’t have large, double blind, placebo controlled, prospective studies of HF patients in sinus rhythm to search for efficacy of antiplatelet agents in reducing ischemic stroke risk (9). Comment of European Society of Cardiology (ESC) HF guidelines published in 2016 on oral anticoagulant and antiplatelet agents is as follows; no antiplatelet therapy other than patients with accompanying CAD whereas there is a substantial risk of gastrointestinal bleeding particularly in elderly patients, in patients with AF and venous thromboembolism oral anticoagulant agents should be used (35). Anticoagulant agents may potentially be considered for intracardiac thrombus, prolonged immobilization/bed rest and for patients accompanying right heart failure and pulmonary hypertension (9).

An important question that has been tried to be addressed by the medical community in the field is the issue “preventing stroke in heart failure patients with sinus rhythm”. Recently, a systematic review and me-

**Table 1. Baseline characteristics of patients with HF in sinus rhythm randomised to anticoagulation therapy or control**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>WASH (37)</th>
<th>HELAS (38)</th>
<th>WATCH (39)</th>
<th>WARCEF (40)</th>
<th>COMMANDER-HF (41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year</td>
<td>2004</td>
<td>2006</td>
<td>2009</td>
<td>2012</td>
<td>2018</td>
</tr>
<tr>
<td>Study design</td>
<td>Open label, controlled</td>
<td>Double blind randomised placebo controlled</td>
<td>Double blind, randomised, double dummy controlled for antiplatelet or open label warfarin</td>
<td>Double blind, randomised, double dummy controlled trial</td>
<td>Double blind, randomised, placebo controlled trial</td>
</tr>
<tr>
<td>Main inclusion criteria</td>
<td>HF requiring diuretic</td>
<td>HF NYHA II-IV</td>
<td>Symptomatic HF, diuretic + ACEI &gt; 60 days</td>
<td>HF NYHA I-IV</td>
<td>HF ≤ 3 months duration, CAD, recent WHF, elevated natriuretic peptides</td>
</tr>
<tr>
<td>LVEF inclusion criteria</td>
<td>≤35%</td>
<td>&lt; 35%</td>
<td>≤35%</td>
<td>≤35%</td>
<td>≤40%</td>
</tr>
<tr>
<td>Randomised (n)</td>
<td>279</td>
<td>197</td>
<td>1587</td>
<td>2305</td>
<td>5022</td>
</tr>
<tr>
<td>Therapies evaluated</td>
<td>Warfarin vs. aspirin vs. no antiplatelet</td>
<td>Warfarin vs. placebo vs. aspirin</td>
<td>Warfarin vs. aspirin vs. clopidogrel</td>
<td>Warfarin vs. aspirin</td>
<td>Rivaroxaban vs. placebo</td>
</tr>
<tr>
<td>Target INR</td>
<td>2-3</td>
<td>2-3</td>
<td>2.5-3</td>
<td>2.3-5</td>
<td>NA</td>
</tr>
<tr>
<td>Aspirin dose (mg/day)</td>
<td>300</td>
<td>325</td>
<td>162</td>
<td>325</td>
<td>NA</td>
</tr>
<tr>
<td>Location</td>
<td>USA and UK</td>
<td>Greece, Cyprus, Yugoslavia, Romania, Bulgaria, Poland and Georgia</td>
<td>USA, UK and Canada</td>
<td>North America, Europe, Argentina</td>
<td>Europe, North America, Latin America, Asia-Pacific, South Africa</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Composite outcome of death, non-fatal MI, non-fatal stroke</td>
<td>Composite of non-fatal stroke, peripheral or pulmonary embolism, MI, rehospitalization, WHF, ACM</td>
<td>Composite of ACM*, non-fatal MI, non-fatal stroke</td>
<td>Time to first event in a composite end point of ischemic stroke, ICH, ACM</td>
<td>Composite of ACM, non-fatal MI and non-fatal stroke</td>
</tr>
</tbody>
</table>

ACM: All-cause mortality, WHF: Worsening HF, NA: Not applicable
ta-analysis of randomized controlled trials on oral anticoagulation versus antiplatelet or placebo for stroke prevention in patients with HF and sinus rhythm was published (36). The authors focused on five studies, summarized in table 1. They concluded that oral anticoagulation is associated with a considerable reduction of stroke risk, which is offset by a significant risk in major bleeding. The authors calculated that for every 1000 patients treated with oral anticoagulation rather than antiplatelet or no antithrombotic treatment for 2.21 years, 13 strokes are prevented but 20 additional major hemorrhages occurred without significant decrease in death rates (36) (Table 1).

Beggs et al (42) recently performed a similar review and meta-analysis of anticoagulation therapy in heart failure and sinus rhythm. They also pointed out the same five clinical randomised trials to address the issue. These trials were the Warfarin/Aspirin Study in Heart Failure (WASH) trial (37), the HEArt failure Long term Antithrombotic Study (HELAS) (38), the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) (39), Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) (40), Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, MI, or Stroke in patients with HF and CAD Following an Episode of Decompensated HF (COMMANDER HF) (41). In this metaanalysis they found no effect on all-cause mortality, no effect on nonfatal MI. There was no effect of anticoagulation therapy on (re)hospitalisation for HF. There was a significant decrease in non-fatal stroke which was offset by major hemorrhage.

COMMANDER HF (41) was the largest study in the meta-analysis performed by Beggs et al. Also, it was the only randomised trial with a non-vitamin K antagoulon (NOAC) in the given context of HF-sinusal rhythm patients. CAD-HF patients received nist oral anticoagulant (NOAC) in the given context of the only randomised trial with a non-vitamin K antago-

Conclusion

Cerebral blood flow abnormalities occur in HF. HF is a major risk factor for thromboembolic events. Use of oral anticoagulants in HF are justified in their well-known indications namely AF, history of a thromboembolic event and intracardiac thrombi.

REFERENCES