



Heart failure and cerebral ischemia

Tamer Sayın and Çetin Erol

Ankara University, School of Medicine, Department of Cardiology, Ankara, Turkey

Corresponding Author:

Çetin Erol, Professor, MD, e-mail: ctnerol@yahoo.com

Heart failure patients may have impaired cerebral autoregulation and regional cerebral blood flow abnormalities. Predisposition 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

Cerebral blood flow, autoregulation mechanisms, heart failure

Weight of the brain is only approximately 2% percent of our body while its metabolic rate accounts close to 20% of the whole body (1). Despite such a high metabolic rate the amount of intracellular glycogen in the brain is low therefore a stable supply of cerebral blood flow (CBF) is critical to maintain normal brain functions. CBF is regulated by both local and systemic mechanisms (2).

The brain is far less tolerant to fluctuations in blood flow because of its dependence on aerobic metabolism and constraints imposed by bipedal posture on blood supply (3). Studies have shown that brain perfusion is maintained and regulated by the help of three mechanisms: neurovascular coupling, cerebral vasoreactivity and cerebral autoregulation.

Neurovascular Coupling

Regional flow differences, for differing functional activity of brain regions so as to compensate the increased metabolic demand of the specific region is called neu-

rovascular 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-

ture could result in as much as a 50% drop in systolic blood pressure and vasovagal syncope. There are strong data to support the role of autonomic nervous system in cerebrovascular regulation (3).

Using transcranial Doppler and magnetic resonance flow/perfusion studies, there are data indicating that even mild heart failure patients may have impaired dynamic cerebral autoregulation and regional perfusion abnormalities (6, 7).

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 (HrEF) 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 HrEF 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 annular 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 randomised 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 Patients 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-

cupitation to thrombogenesis is related with a combination 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 anticoagulant 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 precipitate thromboembolic complications. In patients with HF impaired synthesis of endothelium derived nitric oxide may promote monocyte and platelet adhesion to endothelium (23). Biological markers of endothelial dysfunction and rheologic markers of thrombogenicity-, a hypercoagulable state indicators such as von Willebrand factor, thrombomodulin, soluble e-selectin are found to be consistently elevated in patients with HF (24–26).

A high prevalence of anemia and iron deficiency is reported in patients with HF that may additionally predispose to thrombosis (27). Elevated levels of erythropoietin which is commonly found in anemic – iron deficient patients, iron deficiency related reactive thrombocytosis, increased platelet aggregation as a result of oxidative stress are the proposed components of iron deficient anemic patients' predisposition to thromboembolic 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 ischemic 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 apparent 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 echocardiography to evaluate for a patent foramen oval should be undertaken as well as a Holter rhythm study to exclude paroxysmal atrial fibrillation or flutter. For an undetermined etiology of stroke, it may be necessary to check for intrinsic hypercoagulability test.

In a systematic review of embolic stroke of undetermined source, the authors concluded that so as to define 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, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent myocardial infarction (<4 weeks), LVEF <30%, valvular vegetations or infective endocarditis (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 recordings (9, 30).

Imaging

In an transthoracic echocardiographic (TTE) study, intracardiac thrombi would seem as echogenic, dense, heterogeneous convex masses with clear margins. It can appear as sessile or pediculated, locates close to thin dyskinetic ventricular segments or in the atrial appendage. 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 endothelialized or mobility would affect treatment decisions and responsible clinician should proceed accordingly.

In some certain circumstances, a transesophageal echo (TEE) study may help to have additional diagnostic 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 they have explored thrombus in 25% of patients (32).

Other than a visible thrombus, well known potential cardioembolic sources are; catheter leads, central lines, prosthetic valves, patent foramen ovale, spontaneous echocontrast, thin mobile mitral strands, mitral stenosis, LV systolic and diastolic dysfunction and perhaps pulmonary vein ablation-isolation (33). In a study of ischemic 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 clinical 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

Characteristics	WASH (37)	HELAS (38)	WATCH (39)	WARCEF (40)	COMMANDER-HF (41)
Publication year	2004	2006	2009	2012	2018
Study design	Open label, controlled	Double blind randomised placebo controlled	Double blind, randomised, double dummy controlled for antiplatelet or open label warfarin	Double blind, randomised, double dummy controlled trial	Double blind, randomised, placebo controlled trial
Main inclusion criteria	HF requiring diuretic	HF NYHA II-IV	Symptomatic HF, diuretic + ACEI > 60 days	HF NYHA I-IV	HF ≤ 3 months duration, CAD, recent WHF, elevated natriuretic peptides
LVEF inclusion criteria	≤35%	< 35%	≤35%	≤35%	≤40%
Randomised (n)	279	197	1587	2305	5022
Therapies evaluated	Warfarin vs. aspirin vs. no antiplatelet	Warfarin vs. placebo vs. aspirin	Warfarin vs. aspirin vs. clopidogrel	Warfarin vs. aspirin	Rivaroxaban vs. placebo
Target INR	2-3	2-3	2.5-3	2.-3.5	NA
Aspirin dose (mg/day)	300	325	162	325	NA
Location	USA and UK	Greece, Cyprus, Yugoslavia, Romania, Bulgaria, Poland and Georgia	USA, UK and Canada	North America, Europe, Argentina	Europe, North America, Latin America, Asia-Pacific, South Africa
Primary end point	Composite outcome of death, non-fatal MI, non-fatal stroke	Composite of non-fatal stroke, peripheral or pulmonary embolism, MI, rehospitalization, WHF, ACM	Composite of ACM**, non-fatal MI, non-fatal stroke	Time to first event in a composite end point of ischemic stroke, ICH, ACM	Composite of ACM, non-fatal MI and non-fatal stroke

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 antagonist oral anticoagulant (NOAC) in the given context of HF-sinusal rhythm patients. CAD-HF patients received rivaroxaban 2.5 mg bid or placebo in addition to their antiplatelet therapy. The primary outcome, a composite of first occurrence of death, stroke or MI was negative.

Heart Failure – Sinus Rhythm – Risk of Stroke: Need for Identifying a Higher Stroke Risk Subgroup?

Current data, in preventing stroke, using oral anticoagulants, in HF with sinus rhythm without well-known compelling indications (previous thromboembolism, intracardiac thrombus etc.) is negative. Some authors advocate using some kind of risk models to identify higher risk patients so that use of oral anticoagulants would be justified (9). A nationwide prospective cohort study tried to address this issue (43). The authors used well-known CHA₂DS₂VASc stroke risk prediction model of AF to predict ischemic stroke, thromboembolism, and death in patients with heart failure with or without atrial fibrillation. They concluded that among patients with incident HF with or without AF, the CHA₂DS₂VASc score was associated with risk of ischemic stroke, thromboembo-

lism and death. At high CHA₂DS₂VASc scores (≥4) absolute risk of thromboembolism was high regardless of presence of AF. However, they also found that predictive accuracy was modest and they claimed that clinical utility of CHA₂DS₂VASc score in patients with HF needs to be determined.

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.

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