

The Brain in Heart Failure

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Abstract

After atrial fibrillation, heart failure is the second most frequent cardiac association of stroke. Deteriorating left ventricular systolic function appears to increase the risk of cardioembolic stroke in heart failure. Age, hypertension and prior stroke are also risk factors for stroke in heart failure. Since these are risk factors for cerebral and other vascular disease rather than for cardioembolism, embolism may not be the sole pathogenesis of stroke in heart failure. Hypoperfusion as a cause of cerebral injury is suggested by a reduction of blood flow and autoregulatory capacity in severe heart failure. An increase in cerebral infarct volume and impaired cognition in patients with left ventricular systolic dysfunction also supports this. There is a need for further research to define how the brain is affected by progressive cardiac failure and to determine which echocardiographic and other vascular risk factors best indicate an increased stroke risk.

Keywords

Heart failure, congestive, ventricular ejection fraction, brain ischemia, brain infarction, cognition

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Cardiomyopathy, ejection fraction and heart failure

Ejection fraction (EF) is the proportion of left ventricular volume emptied during ventricular systole. It is a reliable measure of left ventricular systolic function that can be assessed non-invasively by echocardiography or by gated radionuclide scanning; the normal value is 50-70%. When left ventricular systolic function is impaired, EF declines unless there is a corresponding reduction in workload, as occurs in states of peripheral vasodilatation or valvular regurgitation. Consequences of low EF include elevated left ventricular filling pressure and a fall in stroke volume that reduces systemic blood flow. Peripheral vasoconstriction often develops to a degree beyond that required to compensate for the fall in cardiac output and maintain blood pressure. Furthermore, the reduced stroke volume creates a condition of relative stasis within the left ventricle that may activate coagulation processes and increase the risk of thromboembolic events.

Although patients with low EF are prone to hemodynamic decompensation, clinical heart failure is not invariably present. Conversely, cardiac failure may occur in patients with a normal ejection fraction, particularly when the diastolic relaxation properties of the left ventricle are impaired as in cases of hypertrophic cardiomyopathy.

The term *cardiomyopathy* refers to a group of diseases of myocardium that impair cardiac performance. The etiology of cardiomyopathy may be ischemia or infarction on the basis of coronary artery disease, or nonischemic as a result of genetic or acquired defects of myocardial cell structure or metabolism. *Ischemic* cardiomyopathy is particularly common among diabetics and others prone to atherosclerosis, whereas *nonischemic* cardiomyopathy may result from exposure to toxins like alcohol or viral infection.

Congestive heart failure is a clinical syndrome characterized by varying degrees of dyspnea, abnormal fluid accumulation and fatigue. Traditionally, stratification of the severity of functional impairment due to heart failure in clinical studies is based on the New York Heart Association (NYHA) classification. This simply translates tolerance of physical activity such that NYHA class IV refers to heart failure symptoms at rest, class III patients have symptoms on mild exertion, class II have symptoms with moderate effort, and with class I the patient is asymptomatic except at extremes of effort.

Table 1: Echocardiographic findings in 103 patients with dilated cardiomyopathy[†]

Finding	No LV thrombus (n=91)	LV thrombus (n=12)	p-value
LA end systolic diameter (mm)	44 ± 1	50 ± 2	0.03
LV end systolic internal dimension (mm)	56 ± 0.8	60 ± 1	0.04
LV end diastolic internal dimension- (mm)	66 ± 0.6	66 ± 1.0	NS
Interventricular septum thickness (end diastolic) (mm)	12 ± 0.4	12 ± 0.7	NS
LV posterior wall thickness- end diastolic (mm)	11.9 ± 0.3	12.3 ± 0.9	NS
Ejection fraction (%)	22 ± 0.8	13 ± 0.9	0.001
Fractional Shortening (%)	15 ± 0.6	11 ± 2	0.03
Mitral regurgitation jet area (cm ²)	6.2 ± 0.6	3.0 ± 1	0.04
Left atrial area (cm ²)	24.6 ± 1	28 ± 2	NS
Ratio (MR jet area/LA area)	0.26 ± 0.1	0.11 ± 0.1	0.02
<i>Mitral regurgitation:</i>			
None (n [%])	42 [46]	5 [42]	NS
Any MR	49 [54]	7 [58]	NS
Mild	18 [20]	5 [42]	NS
Moderate	20 [22]	2 [17]	NS
Severe	11 [12]	0	NS

Stroke in patients with impaired left ventricular function

Cardiac disease is a major independent risk factor for stroke, ranking third after age and hypertension. In the USA, atrial fibrillation is the most frequent cardiac disorder associated with stroke. Cardiac failure ranks second as a cause of stroke, although it affects about twice the number of individuals in the population than are affected by atrial fibrillation. This is because the rate of stroke in cardiac failure is substantially lower in heart failure (1.6% per year) than in atrial fibrillation (about 5% per year). Atrial fibrillation carries an overall four-fold relative risk of stroke.¹ The relative risk of stroke associated with congestive heart failure is also about fourfold among persons 50 to 59 years of age but diminishes to about x 1.5 by age 80 to 89 years.² The risk of stroke is slightly higher among men with cardiac failure than women, but impaired left ventricular function (as measured by low EF) may be a more powerful risk factor for stroke in women.³ This may reflect sex-related differences in the pathogenesis of heart failure⁴ and consequently of stroke in patients with heart failure. Patients with cardiac failure who have had a stroke have a much higher subsequent stroke rate: 45% five-year (average 9% per year) recurrent stroke rate.⁵

Echocardiographic markers for mural thrombus and embolism

Several echocardiographic markers of ventricular thrombus formation and thromboembolism have been defined in patients with heart failure. Left atrial end-systolic internal diameter and left ventricular internal end-systolic dimension are greater in patients with left ventricular thrombus and EF, fractional shortening, mitral regurgitation jet area and the ratio of mitral

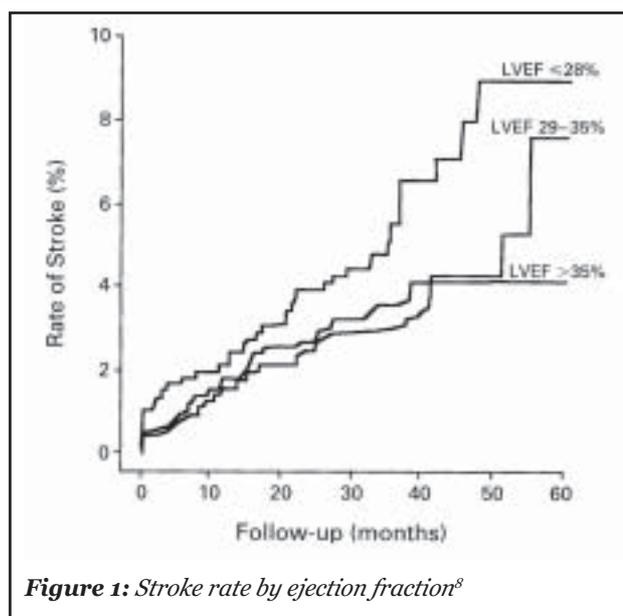


Figure 1: Stroke rate by ejection fraction⁸

regurgitation jet area to left atrial area are significantly decreased in patients with LV thrombus⁶ (Table 1). These findings suggest that both the left atrium and the left ventricle may give rise to thrombi in heart failure. Ischemic etiology and decreasing ejection fraction were the only two risk factors for systemic embolization in another echocardiographic study⁷ (Table 2). Two large studies found the rate of stroke to be inversely proportional to EF.^{3,8} In the Survival and Ventricular Enlargement (SAVE) study,⁸ patients with EF 29-35% (mean 32%) had a stroke rate of 0.8% per year; the rate in patients with EF <28% (mean 23%) was 1.7% per year. There was an 18% increment in the risk of stroke for every 5% decline in EF (Figure 1). These findings apply mainly to men, who represented

Table 2: Multivariate predictors of systemic embolization in severe LV dysfunction⁷

Predictors (18/114pts)	Odd Ratio	p-value
Ischemic etiology	3.79 (1.13-12.64)	0.03
EF%	0.91 (0.82-1.00)	0.04
LVIDD,mm	1.04 (0.98-1.10)	0.18
Age, yr	1.03 (0.97-1.08)	0.38
Apical aneurysm	2.46 (0.40-14.99)	0.56
Atrial fibrillation	1.19 (0.26-5.41)	0.82
Male gender	0.87 (0.22-3.42)	0.84

over 80% of trial participants. A retrospective analysis of data from Studies of Left Ventricular Dysfunction (SOLVD)³, which excluded patients with atrial fibrillation, found a 58% increase in risk of thrombo-embolic events for every 10% decrease in EF among women (p=0.01). There was no significant increase in stroke risk among men in that trial (Table 3). The stroke rate was about 1.4% per year in men with EF \geq 30%. In women the stroke rate was 1.4% per year with EF 21-30% increasing to 2.4% per year with EF \leq 10%.³

Stroke Subtype and vascular risk factors in heart failure

Cardiogenic embolism is thought to be the principal cause of stroke in patients with heart failure. About twelve percent of patients with cardiomyopathy have left ventricular thrombi on echocardiography.⁶ In nonischemic dilated cardiomyopathy, stasis of blood in the poorly functioning left ventricle is thought to predispose to ventricular thrombus formation. Impaired left ventricular function or clinical congestive heart failure increase the risk of stroke in patients with atrial fibrillation.⁹ In ischemic cardiomyopathy, regional ventricular asynergy is a potential

Table 3: Low EF and thromboembolism³

LVEF	Incidence	RR (95% CI)
Men (n=5,457)		
\geq 30%	1.70	1.00
21%-30%	1.83	1.08 (0.83-1.41)
11%-20%	2.01	1.21 (0.86-1.70)
\leq 10%	1.96	1.21 (0.30-4.92)
Women (n=921)		
\geq 30%	1.78	1.00
21%-30%	2.41	1.35 (0.74-2.47)
11%-20%	3.80	2.17 (1.10-4.30)
\leq 10%	4.20	2.43 (0.32-18.26)

Adapted, with permission, from Dries et al. (13). CI=confidence interval; LVEF=left ventricular ejection fraction; RR=relative risk

source of cardioembolic stroke. Patients with ischemic cardiomyopathy however, often have vascular risk factors and atherosclerosis of the arteries supplying the brain. Although vascular risk factors are not known to be direct risk factors for cardiogenic embolism, they appear to be important risk factors for stroke in heart failure. In patients with heart failure without atrial fibrillation, SOLVD found that in men, every 10 years increase in age increases the risk of thromboembolism by a relative risk of 1.3, a history of hypertension also increases the risk of stroke by 1.3, diabetes increases the risk by 1.7 and prior stroke by a risk factor of 2.6. In women with heart failure but without atrial fibrillation, the relative risk of stroke is increased by diabetes (x2.3) and smoking history (x2.4) (Table 4).³ The way by which these risk factors increase the risk of stroke in heart failure is unclear. Patients with these risk factors have a high prevalence of systemic, cervical and cerebral arterial

Table 4: Relative Risk of thrombo-embolic events by gender in studies of left ventricular dysfunction³

	Men (n=5,457)		Women (n=958)	
	RR (95% CI)	p-value	RR (95% CI)	p-value
Age, per decade	1.29 (1.12-1.48)	0.007	1.07 (0.80-1.42)	0.27
EF, per 10% decrease	0.99 (0.81-1.22)	0.95	1.47 (0.97-2.23)	0.07
History of hypertension	1.30 (1.00-1.69)	0.05	1.04 (0.57-1.88)	0.90
Smoking history, yes/no	0.93 (0.68-1.28)	0.65	2.42 (1.24-4.72)	0.01
Diabetes, yes/no	1.71 (1.29-2.28)	0.0002	2.32 (1.24-4.34)	0.009
Previous CVA	2.58 (1.78-3.76)	0.0001	2.34 (0.96-5.71)	0.06
Previous MI	0.77 (0.57-1.03)	0.08	0.75 (0.41-1.36)	0.34
Enalapril vs placebo	0.80 (0.62-1.04)	0.09	0.67 (0.38-1.21)	0.18
Antiplatelet monotherapy	0.71 (0.53-0.94)	0.02	0.37 (0.18-0.84)	0.84
Anticoagulant monotherapy	0.92 (0.59-1.42)	0.69	1.09 (0.44-2.71)	0.84
Antiplatelet and anticoagulant	1.53 (0.80-2.93)	0.21	2.98 (0.67-12.39)	0.15

disease with the potential for cervical or intracranial stenosis and impairment of autoregulation. There may be interplay between severity of arterial disease and decreased cerebral perfusion in these patients. In patients with atrial fibrillation or with recent myocardial infarction, increasing age, prior stroke, hypertension and diabetes, increase the risk of stroke (Table 5).⁹ These data suggest that not all strokes in patients with cardiac failure are of cardioembolic origin.

Hypoperfusion-related cerebral ischemia

Hypoperfusion as a cause of cerebral injury in heart failure is supported by ¹³³Xenon studies¹⁰ that show a lower cerebral blood flow in patients with cardiac failure than in controls. The brain is protected from normal variations in systemic blood pressure by autoregulation, which maintains cerebral blood flow constant unless systemic hypotension is severe. Blood pressure is usually well-maintained in heart failure, but patients with severe left ventricular systolic dysfunction are prone to transient hypotension secondary to cardiac ischemia, arrhythmia or overmedication. Cerebral injury from hypoperfusion may still occur without systemic hypotension if cerebral autoregulation is impaired. Autoregulation appears to be increasingly impaired as patients progress from NYHA class I to class IV cardiac failure.¹¹ Old age, recent stroke or severe carotid occlusive disease also impair cerebral autoregulation in patients without cardiac failure, and patients with cardiac failure who fall into these categories may be particularly at risk for hypoperfusion-related cerebral ischemia.

In order to determine if high-grade cervical or intracranial arterial stenosis increases the risk for hypoperfusion-related cerebral ischemia in patients with heart failure, we compared mean infarct volume on CT or MR hard-copy images between

Table 5: Risk factors for cardiogenic embolism

Risk Factor	Atrial Fibrillation ⁹	Myocardial Infarction ³²	LV Systolic Dysfunction
Hypertension	+	+	+
Diabetes	+	+	+
Prior stroke	+	+	+
Age	+	+	+
Prior MI	+/-	-	+

serial patients with cardiac EF 35% who had high-grade ($\geq 70\%$) carotid artery stenosis and a control group of serial patients with normal cardiac EF and $\geq 70\%$ carotid artery stenosis. In the patients with high-grade carotid stenosis, the mean volume of infarcts ipsilateral to the stenosis was greater in patients with low EF (74.7ml; 95% CI: 17.3-132.1ml) than in patients with normal EF (17.1ml; 95% CI: 9.4-24.8ml) using all infarct types ($p < 0.05$). Frequency of hypertension was the same in these two groups suggesting that low cardiac output may directly cause cerebral hypoperfusion distal to high grade arterial stenosis (Figure 2). We did not find a difference in the number of infarcts between the two groups which suggested that hypoperfusion secondary to low cardiac output tends to increase the size of infarcts caused by other mechanisms, rather than produce infarcts *de novo*.

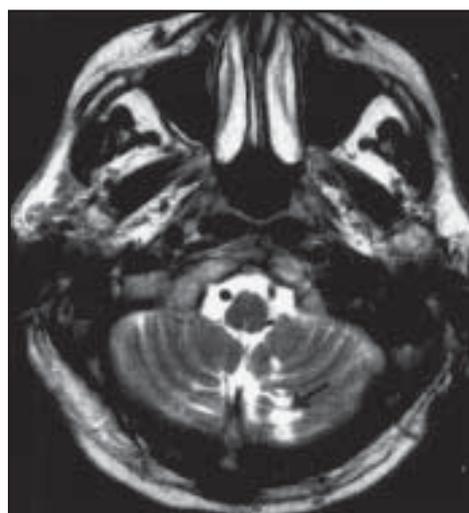
Progressive cerebral injury and “circulatory” dementia

There is evidence of progressive cerebral injury in patients with heart failure. A higher frequency of cortical and ventricular

Figure 2: Watershed cerebellar infarct in patient with ejection fraction 30% and hypoplastic vertebral artery



a) Magnetic resonance angiogram of circle of Willis showing hypoplastic stenosed vertebral artery with posterior inferior cerebellar artery originating from it (arrow)



b) Magnetic resonance brain scan showing a linear infarct (arrow) in the watershed between the areas of supply of the medial and lateral branches of the posterior inferior cerebellar artery, ipsilateral to the stenosed vertebral artery shown in (a)

atrophy is seen in patients with cardiomyopathy.^{12,13} Cardiac failure may also be a risk factor for white matter periventricular ischemic lesions on brain CT scans. A magnetic resonance spectroscopy study found cerebral metabolic abnormalities including the occipital N-acetylaspartate level to be powerful predictors of *cardiac* mortality,¹⁴ establishing a new, important link between cardiac and cerebral dysfunction. These data suggest that as cardiac output decreases, the severity of resulting brain injury mirrors the severity of cardiac disease.

Cognitive impairment is being increasingly recognized as an important complication of heart failure. Patients with end-stage heart failure awaiting heart transplantation have a high frequency of cognitive impairment.¹⁵ Cardiac rehabilitation patients have a high frequency of cognitive impairment.¹⁶ It is unclear from these studies whether the cognitive impairments were due to multiple cerebral emboli or cerebral hypoperfusion. Two studies which excluded obvious stroke, however, suggested that stroke is not necessary to produce cognitive impairment. The first of these found a correlation between the Mini Mental State Examination score and left ventricular ejection fraction in elderly (mean 76.7 years) patients with chronic heart failure.¹⁷ A second population study of patients 65 and older found that cardiac failure is independently associated with cognitive impairment.¹⁸ These studies suggest that hypoperfusion alone may cause cognitive impairment in heart failure. This is also supported by a recent study that found an association between systolic hypotension and cognitive impairment in older patients with heart failure.¹⁹

Memory and attention deficits appear to be the most frequent cognitive deficits seen in heart failure patients followed by slowed motor response time and difficulties in problem solving.²⁰ Verbal memory deficits increase with worsening heart failure class.²¹ Improvement in cognition has been noted following cardiac transplantation.¹⁵ Since heart failure affects some 4.5 million Americans and heart failure and cognitive impairment are frequent among elderly discharged from hospital,²² "Circulatory Dementia"¹⁶ may be a major unrecognized contributor to cognitive impairment in the elderly. Cerebral blood flow may improve with angiotensin converting enzyme inhibitors^{10,23,24} and further studies are needed to determine the prevalence of "circulatory dementia" and to evaluate any therapeutic options.

Anticoagulation in patients with cardiac failure

One of longest-standing unanswered questions in cardiology is whether warfarin is indicated for stroke prevention in patients with heart failure. The place of anticoagulation in patients with heart failure has been controversial since the early 1950s when three randomized controlled studies of coumarin anticoagulants²⁵⁻²⁸ suggested a marked reduction in pulmonary embolism, a halving of mortality and a reduction of thromboembolic events and stroke. The lack of proper randomization, inclusion of patients with atrial fibrillation and

lack of CT imaging however, makes those studies inadequate as a basis to recommend anticoagulation. Since the stroke rate is so low in heart failure (1.6% per year compared with 5% per year in atrial fibrillation), a very large and expensive study (around 8,000 patients) is theoretically needed to determine whether warfarin reduces stroke in heart failure. Routine chronic use of warfarin in patients with reduced ejection fraction would require that the benefits of warfarin outweigh its hemorrhagic risks. The rate of intracerebral hemorrhage is about 0.3% per year with warfarin and about 0.2% with aspirin.²⁹ Even if warfarin reduced stroke by 50% over aspirin (the rate found in atrial fibrillation studies), since the stroke rate is so low in heart failure, one could only achieve a 0.5% absolute reduction in stroke rate per year, meaning that 200 patients would need to be treated with warfarin for a year to save one stroke. Even if a statistically significant "biological" effect of warfarin was found over aspirin, this very small absolute risk reduction is clearly not clinically relevant. Cardiologists and internists however continue to anticoagulate patients with heart failure without proper (Class III) clinical trial evidence of a clinically relevant effect of warfarin.

The SAVE study linked stroke risk with low ejection fraction, suggesting that ejection fraction can be used to select patients with cardiac failure at higher risk for stroke.⁸ The Warfarin Antiplatelet Treatment in Chronic Heart Failure (WATCH) was the first modern randomized controlled study of anticoagulation in heart failure. Patients with ejection fraction 35% and heart failure but without atrial fibrillation were randomized to warfarin, aspirin or clopidogrel. The study was terminated prematurely due to inadequate recruitment, but showed a significant reduction in stroke with warfarin compared to antiplatelet therapy with a hazard ratio of about 0.4. In the warfarin arm of the study, the stroke risk reduction was largely offset by intracerebral hemorrhages. Due to the small number of patients enrolled, the statistical power of the study was insufficient to allow the results to be used as a basis for establishing guidelines for anticoagulation use in heart failure. WATCH also showed a significant reduction in heart failure hospitalizations with warfarin over aspirin but showed no difference in mortality between warfarin and aspirin or clopidogrel. A further definitive study is needed to determine whether anticoagulation should be used in heart failure patients.

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study

The WARCEF study is a National Institutes of Health randomized, double-blind controlled clinical trial with a target enrollment of 2,860 patients. WARCEF is comparing a combined primary endpoint of stroke, death and intracerebral hemorrhage between warfarin (INR 2.5-3) and aspirin (325 mg) with a 90% statistical power. Patients with low ($\leq 35\%$) cardiac ejection fraction are eligible in all New York Heart Association classes (I to IV). 20% of patients will have a stroke or TIA within 12 months prior to randomization. Since patients with prior

stroke have a much higher stroke rate than patients without prior stroke (9% versus 1.6%), the inclusion of these patients should increase the number of stroke endpoints in the study and allow the detection of a “biological” effect of one medication over the other on stroke with the 2,860 patient sample size.

Randomized patients receive either active warfarin and placebo aspirin or active aspirin and placebo warfarin. The study is double blinded: all patients receive regular blood draws for INR evaluation. Patients randomized to active aspirin have INR results that are fabricated by a computer-based algorithm to appear as if they were taking warfarin. Treating clinicians receive and adjust INR results for patients on both warfarin and aspirin and manage all patients as if they were on active warfarin.^{30 31}

In addition to detecting a “biological” effect of warfarin or aspirin on stroke, the study will look for subgroups of patients with higher stroke risk, (for example patients with very low ejection fraction, prior stroke, hypertension), in whom there is a clinically relevant stroke risk reduction. On completion of WARCEF, the results will also be amalgamated with the WATCH study results. Together, the results of these trials will attempt to define the place of antithrombotics in heart failure.

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