PERSPECTIVE

Does Heart Failure Confer A Hypercoagulable State? Virchow's Triad Revisited

Gregory Y. H. Lip, MD, FACC, Christopher R. Gibbs, MRCP

Birmingham, England

It is well-recognized that patients with congestive heart failure are at an increased risk of stroke and venous thromboembolism. Nevertheless, stroke, thromboembolism and myocardial infarction have generally been regarded to be end points of secondary importance in large heart failure trials, when compared with mortality or hospital readmissions. It may well have been that the incidence of thrombotic events are underestimated. The problem of thrombus formation (thrombogenesis) in heart failure may therefore be a much more significant problem than is currently recognized.

The pathophysiology of thrombogenesis in heart failure could well be explained in the context of Virchow's original triad. In addition to "abnormal flow" through low cardiac output, dilated cardiac chambers and poor contractility, patients with heart failure also demonstrate abnormalities of hemostasis and platelets (that is "abnormal blood constituents") and endothelial dysfunction ("vessel wall abnormalities"). These abnormalities contribute to a prothrombotic or hypercoagulable state, which increases the risk of thrombosis in heart failure and impaired left ventricular systolic function.

Some observational data are available on the role of anticoagulants in heart failure, and there is sound evidence to support the use of antithrombotic therapy in patients with heart failure and atrial fibrillation. However, there are no large-scale prospective randomized controlled trials of antithrombotic therapy in patients with heart failure who remain in sinus rhythm, although important studies are in progress. Although the results of these studies are awaited, measurement of suitable markers of thrombogenesis might prove to be valuable in identifying "high risk" patients and in determining the nature, duration and intensity of such treatment. Further information is also needed on the predictive value of various markers of hypercoagulability in patients with heart failure, the association between hemostatic variables and the severity of heart failure, and the effects of different treatments. (J Am Coll Cardiol 1999;33: 1424–6) © 1999 by the American College of Cardiology

Congestive heart failure has long been recognized to predispose to stroke and thromboembolism, occurring in up to 30% of patients, and is often the cause of death (1,2). Recent observational data from the studies of left ventricular dysfunction (SOLVD) and V-HeFT studies (3,4) suggest that mild to moderate heart failure is associated with an annual stroke risk of approximately 1.5% (being particularly high in severe heart failure, 4%), compared with a risk of less than 0.5% in those without heart failure. Although the V-HeFT studies (4) only showed a weak relationship between thromboembolic risk and left ventricular ejection fraction, the Survival and Ventricular Enlargement Study (SAVE) (5) recently reported an inverse relationship between stroke risk and ejection fraction, with an 18% increase in stroke risk for every 5% reduction in left ventricular ejection fraction, thus clearly relating thromboembolism to severe cardiac impairment and the severity of heart failure. The stroke risk was also progressive, continuing for the 42-month follow-up period (5).

In large heart failure trials, stroke, thromboembolism and myocardial infarction have generally been regarded to be end points of secondary importance when compared with mortality or hospital readmissions. It may well have been that the incidence of these vascular events, which have a thrombotic basis, was underestimated (6). Indeed, it is possible that the major cause of sudden death in chronic stable heart failure is not related to arrhythmia, but (thrombotic) vascular occlusion (7). The problem of thrombus formation (thrombogenesis) in heart failure may therefore be a much more significant problem than is currently recognized.

Virchow, as long as 150 years ago, recognized three prerequisites for thrombogenesis: 1) abnormal blood flow; 2) abnormalities in the vessel wall; and 3) abnormalities in blood constituents. The pathophysiology of thrombogenesis in heart failure could well be explained in the context of Virchow's original triad. Low cardiac output, aberrant flow

through dilated cardiac chambers and poor contractility may all produce "flow abnormalities" that predispose to intracardiac thrombus formation and subsequent thromboembolism. In left ventricular dysfunction with aneurysm formation, for example, there is both diastolic and systolic bulging or asynergy, resulting in severe stasis of blood, with consequent predisposition towards thrombus formation. The frequency of left ventricular thrombus in patients with ventricular aneurysms at postmortem can range between 14% to 68%, which is consistent with findings at aneurysmectomy (50% to 95%) (1). Despite this, the reported incidence of systemic thromboembolism in patients with left ventricular aneurysm actually demonstrates a wide range, from 0% to 52% (1,8–10). Poor systolic function may also cause stasis of blood within a dilated left ventricular cavity (11) and indeed, thrombus is more common in such patients, particularly when cardiac dysfunction is severe (12).

Abnormalities of the blood vessel and endothelium represent another component of Virchow's triad, and are indeed relevant, because defective endothelial function has been demonstrated in heart failure (13). The impaired release of endothelium-derived nitric oxide (NO) in response to stimuli may contribute to the increased peripheral vasoconstriction that is characteristic of heart failure; the reduced NO may also promote monocyte and platelet adhesion to the endothelium, predisposing to in situ thrombosis and thromboembolism. An alternative method of assessing endothelial function relies on the measurement of specific markers of endothelial damage or dysfunction, such as von Willebrand factor (vWf), where levels are abnormal in cardiac impairment (14,15). The final component of Virchow's triad, that is, abnormalities in blood constituents (such as rheology, hemostatic markers and platelet function), have all been demonstrated in patients with heart failure (14–17). These abnormalities seem to be due to systolic or contractile dysfunction, with little contribution from diastolic dysfunction (15,18).

The proposed mechanisms for these hemostatic abnormalities include the flow disturbances that are associated with heart failure, in view of the correlation between some hemostatic markers and Doppler indices (18) and neuroendocrine activation (14). Furthermore, heart failure is associated with high levels of atrial natriuretic peptide and chronic diuretic use, which may contribute to hemoconcentration, raised hematocrit and corresponding rheological abnormalities. In the SOLVD and V-HeFT studies, 15% of patients with mild to moderate heart failure also had atrial fibrillation, although only 30% to 40% of these patients received oral anticoagulants (19). Although V-HeFT failed to identify atrial fibrillation as an independent risk marker for thromboembolic events (19,20), clearly atrial fibrillation may account for some of the excess risk of stroke in heart failure (21). Atrial fibrillation per se is also associated with abnormalities in hemostasis, which are compatible with a prothrombotic or hypercoagulable state; these have been

related with blood flow abnormalities ("stasis") within the left atrium (22).

Medical treatment for heart failure may reduce mortality by altering thrombogenesis. Angiotensin converting enzyme (ACE) inhibitors, for example, have beneficial effects on platelets, at least in hypertensive patients (23). Although warfarin has been shown to modify hemostatic markers in heart failure (15,17), there have been no published prospective large scale randomized outcome trials to guide clinicians on the use of antithrombotic therapy, particularly in patients with severe cardiac impairment. Some have nevertheless been initiated, such as the Warfarin Aspirin Study in Heart failure (WASH) pilot study (6). The Veterans Administration is also conducting the large Warfarin-Antiplatelet Trial in Chronic Heart Failure (WATCH) in 4,500 patients with NYHA Class II–IV heart failure and ejection fraction 30%, who will be randomized to warfarin, aspirin or clopidogrel (Dr. Barrie Massie, personal communication). The primary outcomes in WATCH will be all-cause mortality, nonfatal myocardial infarction and nonfatal stroke in addition to ischemic events and thromboembolism.

For now, we have to turn to data from observational data, which are usually retrospective, posthoc analyses. Indeed, the evidence of benefit from observational studies is actually conflicting. For example, the SAVE study (5) did demonstrate an overall 81% reduction in total stroke risk in patients treated with anticoagulation and a 56% reduction in those treated with aspirin, and a retrospective analysis of SOLVD (3) suggested that the use of warfarin and aspirin were both associated with a better prognosis. By contrast, the V-HeFT study only reported a low incidence of thromboembolism in mild to moderate heart failure, which was not reduced with warfarin treatment (20).

The presence of the different components of Virchow's triad in heart failure leads to an increased risk of thrombogenesis; in particular, the presence of abnormalities of hemostasis, platelets and endothelial function suggest that heart failure confers a prothrombotic or hypercoagulable state. The abnormalities in these markers in various disease populations (such as atrial fibrillation, vascular disease and heart failure) suggest that a continuum may be present between "normal," statistically increased levels of these markers and overt thrombus formation. If the mechanisms of thromboembolism are therefore not simply mechanical but are also related to an underlying hypercoagulable state, measurement of suitable markers associated with thrombogenesis may perhaps be useful in identifying "high risk" patients and in determining the nature, duration and intensity of antithrombotic therapy. This is pertinent, because many of these markers of thrombogenesis and endothelial dysfunction have already been shown to have prognostic implications, being predictive of mortality and cardiovascular events. Such risk stratification could perhaps be part of much-needed large, prospective randomized trials assessing the efficacy or risks of anticoagulation for patients with heart failure and sinus rhythm. Further information is needed on

the predictive value of these markers in patients with heart failure, the relationship between hemostatic variables and the severity of cardiac impairment and the effects of different treatments for heart failure.

Acknowledgment

Reprint requests and correspondence: Dr. GYH Lip, Haemostasis Trombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham B18 7QH United Kingdom. E-mail: G.Y.H.LIP@bham.ac.uk.

REFERENCES

1. Nixon JV. Left ventricular mural thrombus. Arch Intern Med 1983;143:1567–71.
2. Griffith GC, Stragnell R, Levinson DC, Moore FJ, Ware AG. Study of beneficial effects of anticoagulant therapy in congestive heart failure. Ann Intern Med 1952;37:867–87.
3. Yusuf S. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions. N Engl J Med 1991;325:293–302.
4. Cohn JN, Archibald DG, Zieshe S, Cobb F, Francis G, Tristani F, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of the Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.
5. Loh E, St John Sutton M, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med 1997;336:251–7.
6. Cleland JGF. Anticoagulant and antiplatelet therapy in heart failure. Curr Opin Cardiol 1997;12:276–87.
7. Narang R, Cleland JGF, Erhardt L, et al. Mode of death in chronic heart failure: a request for more accurate classification. Eur Heart J 1996;17:1390–1403.
8. Lapeyre AC, Steele PM, Kazmier FJ, Vlietstra RE, Fuster V. Systemic embolism in chronic left ventricular aneurysm: incidence and the role of anticoagulation. J Am Coll Cardiol 1985;6:534–8.
9. Mullen DC, Posey L, Gabriel R, Singh HM, Flemma RJ, Lepley D. Prognostic considerations in the management of left ventricular aneurysms. Ann Thorac Surg 1977;23:455–60.
10. Schlichter J, Hellerstein HK, Katz LN. Aneurysm of the heart: a correlative study of one hundred and two proved cases. Medicine (Baltimore) 1954;33:43–86.
11. Meltzer RS, Visser CA, Fuster V. Intracardiac thrombi and systemic embolism. Ann Intern Med 1986;104:689–98.
12. Falk RH, Foster E, Coats MH. Ventricular thrombi and thromboembolism in dilated cardiomyopathy: a prospective follow-up study. Am Heart J 1992;123:136–42.
13. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium-dependent vasodilatation is attenuated in patients with heart failure. Circulation 1991;84:1589–96.
14. Sbarouni E, Bradshaw A, Andreotti F, Tuddenham E, Oakley CM, Cleland JG. Relationship between hemostatic abnormalities and neuroendocrine activity in heart failure. Am Heart J 1994;127:607–12.
15. Lip GYH, Lowe GDO, Metcalfe MJ, Rumley A, Dunn FG. Effects of warfarin therapy on plasma fibrinogen, von willebrand factor and fibrin d-dimer in left ventricular dysfunction secondary to coronary artery disease with and without aneurysms. Am J Cardiol 1995;76:453–8.
16. Jafri SM, Ozawa T, Mammen E, Levine TB, Johnson C, Goldstein S. Platelet function, thrombin and fibrinolytic activity in patients with heart failure. Eur Heart J 1993;14:205–12.
17. Jafri S, Mammen EF, Masura J, Goldstein S. Effects of warfarin on markers of hypercoagulability in patients with heart failure. Am Heart J 1997;134:27–36.
18. Lip GYH, Lowe GDO, Metcalfe MJ, Rumley A, Dunn FG. Is diastolic dysfunction associated with thrombogenesis? A study of circulating markers of a prothrombotic state in patients with coronary artery disease. Int J Cardiol 1995;50:31–42.
19. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure: the V-HeFT studies. Circulation 1993;87:Suppl VI:102–10.
20. Dunkman WB, Johnson GR, Carson PE et al. Incidence of thromboembolic events in congestive heart failure. Circulation 1993;87 Suppl VI:94–101.
21. Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. Ann Intern Med 1992;116:1–5.
22. Lip GYH. Hypercoagulability and Haemodynamic Abnormalities in Atrial Fibrillation. Heart 1997;77:395–6.
23. Blann AD, Lip GYH, Islim IF, Beevers DG. Platelet activation in hypertension. J Hum Hypertens 1997;11:607–9.