(3) reported a significant close correlation between the 2-D echocardiographic LV mass and the necropsy LV mass, and we followed the recommendation of the Committee on M-Mode Standardization of the American Society of Echocardiography (2). We believe that M-mode echocardiography with 2-D monitoring in a blinded fashion was sufficient to evaluate LV mass and LV function, especially in nonischemic CHF patients who were the subjects of this study and who had diffuse LV hypokinesis and no focal hypertrophy by 2-D echocardiography. Actually, we have reported that there was a close correlation between LV mass by echocardiography and LV mass by magnetic resonance imaging in patients with essential hypertension (4).

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REFERENCES

1. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. J Am Coll Cardiol 2001;37:1228–33.
2. Sahn D, DeMaria A, Kisslo J, Weyman A. The Committee on M-Mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–83.
3. Devereux RB, Casale PN, Kligfield P, et al. Performance of primary and derived M-mode echocardiographic measurements or detection of left ventricular hypertrophy in necropsied subjects and in patients with systemic hypertension, mitral regurgitation and dilated cardiomyopathy. Am J Cardiol 1986;57:1388–93.
4. Mitsunami K, Inoue S, Maeda K, et al. Three-month effects of candesartan cilexetil, an angiotensin II type 1 (AT1) receptor antagonist, on left ventricular mass and hemodynamics in patients with essential hypertension. Cardiovasc Drugs Ther 1998;12:469–74.

Increased von Willebrand Factor in the Endocardium as a Local Predisposing Factor for Thrombogenesis in Overloaded Human Atrial Appendage

We read with great interest the article by Fukuchi et al. (1), describing immunohistochemical evidence of increased expression of von Willebrand factor (vWF) in the endocardium of "overloaded" human atrial appendages, as a possible mechanism of intra-atrial thrombogenesis. They describe an increase in atrial endocardial vWF expression in patients with mitral valve disease (MVD) and heart failure, but state that the level of vWF expression is unaffected by the presence of atrial fibrillation (AF). Although we welcome the work as an advancement in our understanding of intra-atrial thrombogenesis, we respectfully suggest that Fukuchi et al. (1) may have understated the potential importance of AF and vWF expression in the endocardium of the left atrial appendage (LAA).

Fukuchi et al. (1) did not show a difference in vWF expression by direct comparison of the LAA of MVD and non-MVD (that is, heart failure) patients. In fact, only heart failure patients (n = 4) showed a significant increase in right atrial appendage (RAA) vWF expression compared with other cardiac patients, but all of the heart failure specimens were obtained postmortem, whereas all other cardiac patient specimens were obtained during cardiac surgery. Perhaps the main finding that can be truly relied upon was the detection of a significant difference between LAA and RAA levels of vWF expression in patients with MVD, with greater levels of vWF in the LAA endocardium compared to the RAA. This finding, coupled with the reported correlation between increased levels of vWF expression and the degree of observed platelet adhesion, could suggest a mechanism for left atrial (LA) thrombus development, which is associated with mitral stenosis.

Unfortunately, Fukuchi et al. (1) do not clarify the proportion of MVD patients with mitral stenosis or mitral incompetence, as mitral incompetence is believed to be associated with a reduction in risk of intra-atrial thrombogenesis. In a study using scanning electron microscopy (SEM), we recently reported evidence of more advanced endocardial changes in the LAA compared with the RAA in MVD patients, and among specimens from patients with mitral stenosis when compared to those with mitral incompetence (2). Furthermore, increasing plasma levels of vWF, an established plasma marker of endothelial damage/dysfunction, were seen to correlate with more advanced SEM endocardial changes. There was also a nonsignificant trend toward increased endocardial changes in MVD patients with AF compared to sinus rhythm. Because AF was present in 12 of the 15 MVD patients studied by Fukuchi et al. (1), the possibility arises that the presence of AF itself (or, at least, in combination with mitral stenosis) led to the increase in LAA expression of vWF in their study.

Fukuchi et al. (1) state that the presence of AF appeared not to influence the LAA expression of vWF, but this is based on only four specimens obtained from patients in sinus rhythm, of which at least one was from a postmortem specimen without MVD. In contrast, all 12 LAA specimens from the AF group were taken from live patients with MVD during a Maze procedure; thus, the comparison may be underpowered and poorly standardized. Second, although the comparison of RAA vWF levels was more appropriately powered, standardization between the two groups was again poor, with 12 out of a total of 16 AF patients studied having MVD, compared with only 3 out of 27 sinus rhythm patients. Furthermore, because the LAA is the main site of thrombogenesis in patients with AF, the lack of observed RAA changes may be of limited clinical significance.

Atrial fibrillation, with or without the additional presence of MVD, has been shown to be associated with increased levels of circulating plasma vWF, as well as other markers of thrombogenesis and platelet activation (3). We have demonstrated that peripheral levels of vWF have been shown to be similar to

intra-atrial levels in patients with AF and mitral stenosis (4), and furthermore, elevated levels of vWF in peripheral blood have been shown to independently predict the presence of LAA thrombus visible by transesophageal echocardiography (5). One preliminary report found increased LAA and RAA endocardial expression of vWF, as well as increased expression of tissue factor in atrial macrophages in AF, compared to sinus rhythm (6).

It is an exciting possibility, however, that plasma levels of vWF may be a reflection of increased atrial endocardial production, possibly in association with damaged endocardial integrity and subsequent release into the blood pool, which itself may predispose to intra-atrial thrombus formation. Indeed, plasma levels of vWF are significantly correlated with fibrin D-dimer levels, an index of thrombogenesis in patients with AF (7). The possibility arises that plasma vWF may provide prognostic information regarding thrombogenesis and risk of subsequent thromboembolism and stroke in AF, and levels of hemostatic markers could potentially be used for risk-stratification purposes and guiding appropriate antithrombotic therapy; prospective longitudinal studies would be required to evaluate this possibility.

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REFERENCES

1. Fukuchi M, Watanabe J, Kumagai K, et al. Increased von Willebrand factor in the endocardium as a local predisposing factor for thrombogenesis in overloaded human atrial appendage. J Am Coll Cardiol 2001;37:1436–42.
2. Goldsmith I, Kumar P, Carter P, Blann AD, Patel RL, Lip GYH. Atrial endocardial changes in mitral valve disease: a scanning electron microscopy study. Am Heart J 2000;140:777–84.
3. Li-Saw-Hee FL, Blann AD, Lip GYH. A cross-sectional and diurnal study of thrombogenesis among patients with chronic atrial fibrillation. J Am Coll Cardiol 2000;35:1926–31.
4. Li-Saw-Hee FL, Blann AD, Goldsmith I, Lip GYH. Indexes of hypercoagulability measured in peripheral blood reflect levels in intracardiac blood in patients with atrial fibrillation secondary to mitral stenosis. Am J Cardiol 1999;83:1206–9.
5. Heppell RM, Berkin KE, McLenachan JM, Davies JA. Haemostatic and haemodynamic abnormalities associated with left atrial thrombosis in non-rheumatic atrial fibrillation. Heart 1997;77:407–11.
6. Al-Saady NM, Haven AJ, Maarouf N, et al. Von Willebrand and tissue factor expressions increased in the atrial tissue of the fibrillating atrium (abstr). J Am Coll Cardiol 2001;37 Suppl A:113A.
7. Lip GYH, Lowe GDO, Rumley A, Dunn FG. Increased markers of thrombogenesis in chronic atrial fibrillation: effects of warfarin therapy. Br Heart J 1995;73:527–33.

REPLY

We appreciate the comments by Drs. Conway and Lip on our current study (1). Basically, our data on immunoreactive von Willebrand factor (vWF) in the atrial endocardium are not directly comparable with the data on plasma vWF levels (2,3). Because the latter would reflect some variable factors: that is, endothelial cell- or platelet-origin, constitutive secretion or leakage from damaged cells, and the cause or result of thrombogenesis? However, several points raised in the letter may be important for understanding our data. The first point is related to vWF immunostaining in postmortem atrial tissue. Our study had a limitation in the tissue sampling at heart surgery as described in the Methods section. For comparison, atrial tissue was also obtained at autopsy from heart failure patients and noncardiac patients. The endocardial endothelium showed similar staining for endothelial cell marker CD31, but quite different vWF staining between heart failure patients and noncardiac patients. In addition, the apparent vWF staining in the endothelium of intramyocardial vessels was preserved in all postmortem tissues as seen in the operative tissues (see our Fig. 2). Therefore, there is no reason to consider the data on the postmortem tissue to be weak.

The second point is related to the proportion of patients with mitral stenosis or mitral regurgitation. Strong vWF staining in the endocardium of left atrial appendage was seen in all 10 patients examined, irrespective of mitral stenosis or mitral regurgitation (five patients each). Although the vWF levels in the endocardium may not necessarily reflect a hypercoagulable state in mitral stenosis compared with that in mitral regurgitation, it must be recognized that vWF in the endocardium is only one of the factors involved in intra-atrial thrombogenesis.

The third point is related to the interrelation between atrial fibrillation (AF) and underlying heart disease in intra-atrial thromogenesis. In mitral valvular disease, AF often occurs secondarily to increased mechanical stress to the left atrial wall. It is well known that thromboembolic events occur more frequently in AF patients with underlying heart diseases than in patients with AF alone. Our study showed much stronger vWF staining in the left atrial endocardium than in the right one of AF patients with mitral valvular disease (see our Figs. 1 and 3). In addition, immunoreactive vWF in the right atrial endocardium of cardiac but non-AF patients was significantly increased compared with that of noncardiac patients (see our Fig. 3). Because the conditions of all cardiac patients examined were severe enough to require heart surgery, the atrial wall may have been exposed to overloaded conditions. Thus, we speculate that increased vWF in the endocardium may be associated with mechanical stress to the atrial wall, irrespective of whether AF is present or not. Increased vWF in the endocardium via mediating platelet adhesion to the endocardium would be of limited significance in thrombogenesis. Probably, rheologic factors induced by AF in combination with underlying heart disease are required for the development of thrombi responsible for embolic events (4).

Finally, we emphasize that immunoreactive vWF in the atrial endocardium was increased in patients with severe underlying heart diseases regardless of the presence of AF. This may be important particularly in regulating local thrombogenicity on the endocardial surface.

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