Editorial

Classification Criteria for Antiphospholipid Syndrome: The Case for Cardiac Valvular Disease

The Sapporo classification criteria for antiphospholipid antibody syndrome (APS) were eminence- rather than evidence-based[1]. The most recent revision of the APS classification criteria was presented at the Taormina conference. This revision was evidence-based in that it included requirements: (1) a manifestation must be present in both the primary and secondary forms of APS; (2) it must be be proven by multiple study designs, including retrospective case-control and prospective cohort studies; (3) multiple positive studies (i.e., different research groups) must be available for each study design; and (4) the assays used must meet international criteria for validity.

Using these strict requirements for evidence-based criteria, cardiac valvular disease (thickening or vegetations) should clearly be included in APS criteria. There is a strong pathophysiologic rationale for considering cardiac valve disease as a manifestation of APS[2]. Multiple supportive prospective cohort studies (Table 1A) and case-control studies (Table 1B) exist. Positive associations have been found using both study designs and in both systemic lupus erythematosus (SLE) and non-SLE populations, meeting our criteria for inclusion in evidence-based classification criteria. However, it is necessary for valvular disease to be stringently defined as valve thickening or valve vegetations. The new series from Zavaleta, *et al* in this issue of *The Journal* found cardiac valve lesions in 71% of patients. Over the 5 year followup period, both new lesions and progression of old lesions occurred[3].

The APS classification criteria do not specify the pathogenetic pathways. Thrombophilia is part of APS, certainly. Recent work, however, has elucidated multiple pathogenetic mechanisms of antiphospholipid antibodies. In early pregnancy losses, interference with trophoblast invasion, not thrombosis, is key. The benefit of heparin in late fetal loss may not be due to its anticoagulant effects, but to its antiinflammatory effects[4]. Some neurologic manifestations of APS do not fit the mold of thrombosis, either. Chorea may represent either a metabolic or inflammatory consequence of antiphospholipid binding. Transverse myelitis is more often inflammatory (responding to corticosteroids) than thrombotic.

Is the cardiac valve disease of APS inflammatory or thrombotic? Some histologic studies[5] suggest that fibrin deposits are the major findings, not inflammation. However, antibody deposition and complement components initiating valve damage have been described[2], along with increased endothelial cell expression of alpha 3 beta 1 integrin[6]. Although one case report suggested that anticoagulation

Table 1A. Cardiac valve disease. Prospective cohort studies.

	SLE Cases	Non-SLE Cases	aCL	LAC	Results
APASS, 1997[10]		219	+	0	NS
Tanne, 1999[11]			+	0	NS
Gentile, 2000[12]	91		+	0	Moderate; p = 0.02 Mild; p = NS
Khamashta, 1990[13]	132		+	+	Vegetations; p < 0.001 Mitral regurgitation; p < 0.001
Jouhikainen, 1994[14]	74		0	+	p = 0.05

+: a positive association was found. 0: not studied. aCL: anticardiolipin. LAC: lupus anticoagulant. NS: not significant.

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Table1B. Cardiac valve disease. Case-control studies.

	SLE Cases	Primary APS Cases	Controls	aCL	LAC	Results
Bouillanne, 1996[15]		89	80	+	+	$p < 0.03$
Leung, 1990[16]	75	75	60	+	+	Verrucous; $p < 0.005$ Valve thickening; $p < 0.02$ Mitral regurgitation; $p < 0.001$ Aortic regurgitation; $p < 0.02$
Gabrielli, 1995[17]	39	20	20	+	0	NS
Badui, 1995[18]		20	20	+	0	Mitral thickness; $p < 0.001$ Aortic thickness; $p < 0.001$
Metz, 1994[19]	52		52	+	+	Tricuspid regurgitation; $p = 0.02$

shrank valve vegetations[7], a case series of 13 patients[8] and the 5 year followup study of Zavaleta, *et al*[3] did not find antiplatelet or anticoagulant therapy of benefit. In our experience, a one month course of high dose corticosteroids is given, with followup 2D cardiac echocardiograms to determine the rate of corticosteroid taper, along with anticoagulation to prevent embolic strokes. Others agree that the underlying pathology is a valvulitis, responding to corticosteroids[9].

Cardiac valve disease should now be included in classification criteria for APS. However, its pathogenesis may not be primarily thrombotic, nor should its initial treatment be limited to anticoagulation.

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