

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



The Sapporo classification criteria for antiphospholipid antibody syndrome (APS) were evidence- rather than evidence-based¹. 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 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 APS². 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 occurred³.

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 effects⁴. 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 studies⁵ suggest that fibrin deposits are the major findings, not inflammation. However, antibody deposition and complement components initiating valve damage have been described², along with increased endothelial cell expression of alpha 3 beta 1 integrin⁶. 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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Table 1B. 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 vegetations⁷, a case series of 13 patients⁸ 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 corticosteroids⁹.

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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