# Cardiac Involvement in Granulomatosis with Polyangiitis

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***ABSTRACT.*** ***Objective.*** To determine frequency and outcomes of granulomatosis with polyangiitis (GPA)–related cardiac disease in a North American GPA cohort.

***Methods.*** Analysis was done of all patients in the Vasculitis Clinical Research Consortium Longitudinal Study of GPA. Demographic and clinical characteristics of patients with and without GPA-related cardiac involvement were compared.

***Results.*** Of 517 patients with GPA, 3.3% had cardiac involvement. No differences were observed between patients with or without cardiac involvement in terms of demographics, antineutrophil cytoplasmic antibody positivity, or relapse rate.

***Conclusion.*** Cardiac involvement in GPA is rare and heterogeneous. In this cohort, cardiac involvement was not associated with a higher rate of relapse or premature death. (J Rheumatol First Release May 1 2015; doi:10.3899/jrheum.141513)

*Key Indexing Terms:*
CARDIAC DISEASE GRANULOMATOSIS WITH POLYANGIITIS VASCULITIS

The clinical presentation of granulomatosis with polyangiitis (GPA; previously Wegener granulomatosis) is heterogeneous, and while involvement of the upper and lower respiratory tract and kidneys is typical, any organ system can be affected. Cardiac involvement in GPA has long been regarded as rare, yet a wide spectrum of abnormalities have been reported, including pericarditis, myocarditis, valvular lesions, coronary arteritis, and conduction system defects, with prevalence figures ranging from 5–90% of patients depending on the series and diagnostic methods applied[1,2,3,4,5].

The significance of cardiac involvement in GPA, besides being potentially life threatening, has been highlighted in some cohort studies. The European Vasculitis Study Group determined that cardiovascular involvement [5.7% of 535 newly diagnosed patients with GPA, microscopic polyangiitis (MPA), or renal-limited vasculitis] was an independent risk factor for disease relapse[1]. In the study by Koldingsnes and Nossent[6], involving 56 Norwegian patients with GPA, 20% had cardiac involvement, and cardiac involvement was among several factors associated with an increased risk of initial treatment resistance and disease relapse. Similarly, the French Vasculitis Study Group, using multivariate analysis in a large cohort of patients with GPA and MPA, found that cardiac involvement was a risk factor for poor overall prognosis and increased relapse[2,7]. However, in all of these studies, the precise nature of the

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cardiovascular involvement and the diagnostic tools used were not specified.

We conducted our study to determine the prevalence and nature of cardiac manifestations in patients with GPA followed within a multicenter longitudinal cohort in North America.

## MATERIALS AND METHODS

The data source was the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Study of GPA and MPA. The VCRC is part of the Rare Diseases Clinical Research Network, funded by the US National Institutes of Health. Since 2006, the VCRC has conducted a series of observational longitudinal studies of patients with various systemic vasculitides in vasculitis centers in the United States and Canada. The VCRC database includes demographic, clinical, laboratory, and radiological data collected prospectively every 3 to 12 months on all enrolled patients.

Between May 2006 and January 2013, 517 patients with a diagnosis of GPA according to the modified American College of Rheumatology criteria[8] were enrolled in 9 North American centers. For our study, patients with GPA were considered to have had cardiac manifestations if they had any documented history of cardiac disease deemed by the VCRC investigator to be secondary to GPA at any point over the course of their illness. VCRC investigators were contacted as needed to validate the cardiac GPA diagnosis and/or to obtain more information regarding the presentation and diagnostic tests used.

Patients with and without a history of cardiac involvement secondary to GPA were compared in terms of demographic variables, ANCA status, disease associations, and outcomes (relapses and deaths).

Comparisons between groups were done by means of 2 sample t tests for numerical data and chi-squared or Fisher's exact test for binary datasets. Statistical analyses were performed using Minitab Statistical Software, version 16.1[9].

## RESULTS

*Patient identification and characteristics*. Mean disease duration, as of January 2013, for the 517 patients with GPA was 106 ± 71 months (median 94 mos, range 2–399 mos); 55 (11%) were enrolled within the first 3 months following the diagnosis of GPA.

There were 17 patients (3.3% of the total GPA cohort) documented to have had cardiac manifestations deemed secondary to GPA, and 16 of them had documented cardiac involvement prior to enrollment into the VCRC Longitudinal Study. Patient demographics are listed in Table 1. Nine patients had cardiac involvement as part of their initial presentation of GPA and 7 during disease relapses predating enrollment into the VCRC; the mean time from diagnosis to study enrollment for those 7 patients was 7.4 years (range, 1–18 yrs). Only 1 patient developed cardiac involvement during a disease relapse following study enrollment.

*Cardiac manifestations and diagnostic methods*. Pericarditis was the most common cardiac manifestation (n = 6, 35%), followed by cardiomyopathy (n = 5, 30%), coronary artery disease (CAD; n = 2, 12%), valvular disease (n = 1, 6%), concomitant CAD and valvular disease (n = 1, 6%), concomitant pericarditis and cardiomyopathy (n = 1, 6%), and severe conduction disorder (n = 1, 6%).

All patients with cardiac involvement presented with cardiorespiratory symptoms including chest pain, palpitations, syncope, or dyspnea. None of these manifestations were identified through routine cardiac investigations in asymptomatic patients. Diagnostic methods varied over time and between centers and included electrocardiogram, cardiac enzymes, transthoracic echocardiogram, thoracic computerized tomography, cardiac magnetic resonance imaging (MRI), and coronary angiography.

*Table 1.* Demographics and disease manifestations of patients with granulomatosis with polyangiitis (GPA) with and without cardiac involvement.

| Demographics | GPA with Cardiac Involvement | GPA without Cardiac Involvement | p |
|---|---|---|---|
| Total, n | 17 | 500 | |
| Female, n (%) | 7 (41) | 262 (52) | 0.36 |
| Mean age at diagnosis, yrs (± SD) | 43.7 (16.5) | 45.9 (20.3) | 0.70 |
| Race, n (%) | | | 0.24 |
| White | 17 (100) | 442 (88) | |
| Nonwhite* | 0 | 58 (12) | |
| Time from symptom onset to diagnosis, mos (± SD) | 21 (28) | 14 (36) | 0.48 |
| Duration of followup, mos (± SD) | 97 (67) | 106 (71) | 0.68 |
| ANCA-positive, n (%)** | 16 (94) | 407 (81) | 0.33 |
| Anti-PR3–positive, n (%)# | 11 (65) | 338 (68) | 0.68 |
| Any history of flare† | 9 (53) | 325 (65) | 0.31 |
| Disease manifestations | | | |
| Constitutional | 14 (82) | 400 (80) | 1.0 |
| Musculoskeletal | 10 (59) | 334 (67) | 0.49 |
| Skin | 8 (47) | 158 (32) | 0.12 |
| Mucus membranes | 1 (6) | 57 (11) | 1.0 |
| Eyes | 1 (6) | 163 (33) | 0.03 |
| Ear, nose, and throat | 13 (76) | 431 (86) | 0.28 |
| Lung | 14 (82) | 351 (70) | 0.42 |
| Gastrointestinal | 0 | 7 (1) | 1.0 |
| Kidney involvement | 10 (69) | 275 (55) | 0.55 |
| Nervous system involvement | 4 (24) | 109 (22) | 0.76 |

* Asian/Black/African American/Unknown race/mixed race or American Indian/Native Alaskan. ** Antineutrophil cytoplasmic antibody (ANCA), including cytoplasmic ANCA or perinuclear ANCA. # Antiproteinase 3 antibody. †Any history of flare defined as disease activity after a period of remission, either prior to enrollment in the Vasculitis Clinical Research Consortium (VCRC) or during subsequent VCRC followup.

*Association of cardiac manifestations with other disease manifestations*. The characteristics of patients with and without cardiac involvement and the frequencies of their noncardiac manifestations were comparable (Table 1), except for eye manifestations, which were observed less frequently in the patients with GPA with cardiac involvement.

*Treatment and outcomes*. There were no differences between patients with and without cardiac involvement with regard to treatment with cyclophosphamide (CYC): 71% (n = 12) of patients with cardiac involvement versus 72% (n = 360) of those without cardiac involvement received this drug over

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the course of their disease (p = 1.0). Of the 5 patients with GPA with cardiac involvement who did not receive CYC, the cardiac manifestations included pericarditis (n = 2), CAD (n = 1), CAD with valvular disease (n = 1), and cardiomyopathy with concomitant pericarditis (n = 1); none of these patients received rituximab (RTX), 2 received only glucocorticoids throughout their disease course, and 3 received at least 1 of methotrexate, azathioprine, or mycophenolate mofetil. There was no difference in the proportion of patients treated with RTX: 18% of the group with cardiac disease compared to 17% of the noncardiac disease group (p = 1.0). There was no difference in relapse rates between the 2 groups; 53% (n = 9) of the cardiac disease group had 1 or more relapses throughout the course of their disease compared to 65% (n = 325) of the noncardiac GPA group (p = 0.31). Similarly, there was no difference in mortality between the 2 groups; death was reported in 2% (n = 12) of the group without cardiac involvement and none of the GPA patients with cardiac involvement (p = 1.0).

## DISCUSSION

In this large cohort of patients with GPA, cardiac involvement occurred in 3.3%. There were no obvious specific associations of cardiac disease with other disease manifestations and no difference in outcomes, compared to patients with no cardiac involvement.

The frequency of cardiac involvement observed in this cohort is comparable to that reported by the European Vasculitis Study Group[1] (5.7%) but notably lower than that reported by the French group (clinically evident cardiac disease was seen in 13% of patients with GPA)[2]. Possible reasons for these differences include the heterogeneity of the cohorts, the definition of cardiac manifestations, and the diagnostic methods used. In our current study, the diagnosis of cardiac involvement in GPA was based on clinical, echocardiography, or electrocardiogram findings. With the emergence of readily available cardiac MRI, higher rates of subclinical cardiac involvement are likely to be observed; the clinical significance of these rates remains to be determined as does the appropriateness of performing these investigations in asymptomatic patients.

In contrast with previous European reports, cardiac involvement was not associated in this North American population with a higher rate of mortality or relapse of vasculitis. This finding may in part be explained by the lower frequency of cardiac manifestations observed in the VCRC cohort, thereby limiting statistical power. It is also possible that the global outcomes of patients with GPA have improved over the past decades, with more individually tailored therapeutic regimens and the more systematic use of potent agents such as CYC and RTX[10].

A significant strength of our study is the large number of patients with GPA included in the cohort, the protocolized nature of data collection at expert centers, and the validation of specific details of each patient's history from the treating VCRC investigator, as needed.

Our study had some limitations, including the non-uniform imaging modalities used in each participating center and the absence of systematic collection of electrocardiographic or echocardiographic data. It is also noteworthy that all cardiac manifestations, with the exception of 1, occurred prior to the patients being enrolled in the study.

The longterm followup and study of late cardiovascular complications in patients with GPA was not a specific endpoint of this study. Such late complications are likely more common in GPA than in the general population, as highlighted by a review of a Danish National Hospital register in which patients had an increased rate of myocardial infarction within 5 years of diagnosis of GPA when compared to the general population[11]. This finding was further substantiated by another European retrospective study demonstrating an increased incidence of vascular events in patients with GPA and MPA when matched for renal function and other conventional cardiovascular risk factors[12]. Further longterm observation of the ongoing VCRC cohorts will likely provide additional information on these cardiovascular complications of patients with systemic vasculitis.

GPA-related cardiac manifestations are rare and heterogeneous, with pericarditis being the most frequent. In this cohort, cardiac involvement was not associated with poorer outcomes, possibly as a result of aggressive treatment and close monitoring within vasculitis-specialized centers.

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