Cardiac Manifestations of Acquired Immunodeficiency Syndrome

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Acquired immunodeficiency syndrome is a serious problem worldwide. Recent advances in the knowledge about human immunodeficiency virus (HIV) replication and the treatment of HIV infection have improved survival in HIV patients. Because of the longer survival in HIV patients, the more manifestations of late-stage HIV infection will be seen, including HIV-related cardiac diseases. The common cardiac manifestations in patients with the acquired immunodeficiency virus are pericardial effusion, myocarditis, dilated cardiomyopathy, endocarditis, pulmonary hypertension, malignant neoplasms, and drug-related cardiotoxicity. This review focuses on these cardiac manifestations in patients with the acquired immunodeficiency syndrome.

PERICARDIAL EFFUSION

Pericardial effusion is one of the most common forms of cardiovascular involvement in HIV infection. There are varieties of clinical manifestations, which include asymptomatic pericardial effusion, pericarditis, cardiac tamponade, and constrictive pericarditis. Approximately one fifth of AIDS patients have pericardial effusion.6-11 The pericardial effusion is often small and without hemodynamic consequence; however, large effusion can occur and may cause cardiac tamponade.12-14

The clinical manifestations of pericarditis are similar between patients with and without HIV infection.15 Moreno et al16 reviewed echocardiographic studies in 141 HIV-infected patients, and 55 (39.0%) of them had pericardial effusion. Most (34 of the 55) were small. The clinical presentation of pericarditis was compared between patients with small pericardial effusion and those with moderate to large pericardial effusion. They found that the presence of a pericardial friction rub and electrocardiographic repolarization abnormalities consistent with pericarditis were more often seen in patients with moderate to large pericardial effusions. The reason for these findings is unclear. Specific identifiable causes of pericardial effusion in AIDS patients are not always possible.17,18 The causative factors involved in the development of pericardial effusion have been described. Flum et al18 performed pericardial fluid cultures and pericardial biopsies in 29 AIDS patients with pericardial effusion who underwent a pericardial window procedure. The causes were identi-
Cardiac tamponade. Sunderam et al21 studied a select group of 29 AIDS patients who had M tuberculosis. Of these 29 patients, 21 (72%) had extrapulmonary tuberculosis. Tuberculous pericarditis was found in 1 (5%) of these 21 patients with extrapulmonary tuberculosis. Zuger et al22 reported that 1 (4%) of 26 AIDS patients with cryptococcal infection had pericarditis. Eisenberg et al23 could identify the cause of pericardial effusion in 4 (29%) of 14 AIDS patients with pericardial effusion. The causes included lymphoma (1 patient), myocardial infarction (1 patient), and endocarditis (2 patients). Kaposi sarcoma has been reported to cause pericardial effusion and cardiac tamponade.24 Numerous case reports have shown multiple unusual organisms associated with pericardial effusion in HIV patients (Table 1).

Heidenreich et al24 studied the incidence of pericardial effusion and its relation to mortality in HIV patients. Two hundred thirty-one patients were recruited during a 5-year period, and 74 had AIDS. Fifteen patients with HIV infection had pericardial effusion, and 12 (80%) of these pericardial effusions were small. Only 2 patients (1 with a moderate and 1 with a large pericardial effusion) developed symptoms and signs of cardiac tamponade, which required drainage. Patients with AIDS who have pericardial effusion have a 9% annual incidence of cardiac tamponade, and 1% of all AIDS patients developed cardiac tamponade annually.24 The size of pericardial effusion did not correlate with the shortened survival, but the presence of pericardial effusion did. The mean ± SD 6-month survival was 36% ± 11% compared with 39% ± 3% in AIDS patients without effusion. The CD4 (T-helper lymphocyte) cell count was lower in AIDS patients with effusion than in those without effusion (0.059 vs 0.146 × 10⁹/L).25 Pericardial effusion in HIV patients may be a marker of end-stage HIV infection because it is associated with low CD4 cell count and is often caused by opportunistic infections and malignant neoplasms seen in the advanced state of AIDS. Although pericardial effusion is seen in patients with the advanced stage of HIV infection, it rarely causes death in these patients.

MYOCARDITIS

Anderson et al27 suggested that myocarditis in HIV patients may play a role in the development of ventricular dysfunction. The autopsy incidence of myocarditis was approximately one third of all AIDS patients. A specific cause was found in less than 20% of these patients. Common pathogens in AIDS myocarditis include Toxoplasma gondii, M tuberculosis, and Cryptococcus neoforms. Other infectious organisms have been reported to include Mycobacterium avium-intracellulare complex, Aspergillus fumigatus, Candida albicans, Histoplasma capsulatum, Coccidioides immitis, cytomegalovirus, and herpes simplex.2 Report recent data suggested that HIV alone can cause myocarditis. Either HIV or its proteins (p17, p24, and gp120/160) have been found in the heart specimens of patients with AIDS with or without cardiac diseases by culture, in situ deoxyribonucleic acid hybridization, and by Southern blot tests.38-40 Superantigen plays an important role in the pathogenesis of many diseases by forming a trimolecular complex with major histocompatibility class II molecule on the antigen-presenting cells and the Vβ-specific region on the T-lymphocyte receptor. The binding results in a massive stimulation of the T lymphocyte. The role of superantigen in the pathogenesis of AIDS has been described.31 After the binding of HIV regulatory protein (Nef) with major histocompatibility complex class II on antigen-presenting cells, the T lymphocytes become activated. The activation of T lymphocytes stimulates the proliferation and release of cytokines such as interferon γ and interleukin 2. Therefore, the viral load in the heart will increase from creating a cellular reservoir for HIV. T-lymphocyte depletion may be caused by apoptosis, anergy, or both. Proliferation of the B cell may result in hypergammaglobulinemia. Autoimmune response may occur as a result of B-cell differentiation into immunoglobulin-secreting cells and activation of the T lymphocyte.41

Lymphocytic myocarditis was found in 37 (52%) of 71 patients who died of AIDS.37 There were 3 types of histological features: lymphocytic infiltrate with necrosis of the myocardial fibers, lymphocytic infiltrate without necrosis of the

Table 1. Causative Factors Associated With Pericardial Effusion in Patients With the Human Immunodeficiency Virus

<table>
<thead>
<tr>
<th>Source</th>
<th>y Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flum et al,19 1995 and Decker and Tuazon,19 1994</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Karve et al,20 1992</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Holtz et al,21 1995</td>
<td>Nocardia asteroides</td>
</tr>
<tr>
<td>Ferguson et al,22 1993</td>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Lee-Chiong et al,23 1995 and Legras et al,24 1994</td>
<td>Rhodococcus equi</td>
</tr>
<tr>
<td>Kroon et al,25 1989</td>
<td>Chlamydia trachomatis</td>
</tr>
<tr>
<td>Sunderam et al,26 1986</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Moreno et al,28 1994</td>
<td>Mycobacterium kansasii</td>
</tr>
<tr>
<td>Zuger et al,29 1986</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Zakowski and Janule-Shanerman,30 1993</td>
<td>Histoplasma capsulatum</td>
</tr>
<tr>
<td>Gueret et al,31 1994</td>
<td>Toxoplasma gondii</td>
</tr>
<tr>
<td>Nathan et al,32 1991</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Freedberg et al,33 1987</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Stoka et al,34 1989</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Flum et al,35 1995</td>
<td>Lymphoma and adenocarcinoma</td>
</tr>
<tr>
<td>Eisenberg et al,36 1992</td>
<td>Postmyocardial infarction</td>
</tr>
</tbody>
</table>
myocardial fibers, and focal and mild myocarditis with a mononuclear infiltrate. Reilly et al studied the relation between clinical and histopathological cardiac findings in patients with AIDS. Interestingly, myocarditis was found in all patients with congestive heart failure, left ventricular dysfunction, and ventricular tachycardia. Baroldi et al evaluated the relation between cardiac dysfunction and myocarditis. Of 26 patients with AIDS, 8 underwent postmortem echocardiography. Of these 8 patients, 6 had abnormal cardiac function (abnormal fractional shortening, left ventricular hypokinesis, and diffuse left ventricular dilation). All patients with abnormal echocardiographic findings had lymphocytic myocarditis with or without myocardial necrosis post mortem.

DILATED CARDIOMYOPATHY

In 1986, Cohen et al described the first case of rapidly fatal, dilated cardiomyopathy in a patient with AIDS. The prevalence of dilated cardiomyopathy ranges from 10% to 30% by echocardiographic and autopsy studies. Several prospective clinical and echocardiographic studies have suggested that a subgroup of HIV-infected patients may be predisposed to the development of clinically significant and progressive heart disease. Herskowitz et al found that patients with severe symptomatic heart failure usually had a low CD4 cell count, myocarditis, and a persistent elevation of antineut antibodies. The postmortem gross findings of dilated cardiomyopathy in patients with AIDS have included increased heart weight, with either biventricular or 4-chamber dilation, and a pale-appearing myocardium. Echocardiographic findings included 4-chamber enlargement, diffuse left ventricular hypokinesis, and decreased fractional shortening. Courdray and colleagues demonstrated that left ventricular diastolic impairment could occur in the early stage of HIV infection. Dilated cardiomyopathy occurs late in the course of HIV infection and is usually associated with a significantly reduced CD4 cell count, however, there was no association between the progression of left ventricular dysfunction and the rate of CD4 cell count decline.

The pathogenesis of cardiomyopathy remains unclear. Several studies have supported the direct role for HIV-1-mediated cardiac injury, but the mechanism remains unclear. One hypothesis focuses on the role of an alteration of T-helper cell function inducing myocardial inflammation by uncontrolled hypergammaglobulinemia. The HIV gene may provoke cell surface cardiac muscle protein, resulting in the induction of circulating cardiac autoantibodies, which can trigger a progressively destructive autoimmune reaction.

Selenium deficiency and its association with cardiomyopathy have been described. Case reports of pediatric AIDS patients have shown an improvement of cardiac function after selenium supplementation. Barbaro et al performed a prospective, long-term clinical and echocardiographic follow-up study of 932 asymptomatic HIV-positive patients. An echocardiographic diagnosis of dilated cardiomyopathy was made in 76 patients (8.0%), with a mean annual incidence of 1.59 per 1000 patients during a mean ± SD follow-up period of 60.0 ± 5.3 months. All patients with an echocardiographic diagnosis of dilated cardiomyopathy underwent endomyocardial biopsy within 1 month. They found myocarditis in 63 (83%) of the patients with dilated cardiomyopathy on histological examination, and 36 (57%) of the patients with myocarditis had a positive hybridization signal for HIV nucleic acid sequences. Among these 36 patients who had myocarditis and a positive hybridization signal for HIV nucleic acid sequences, 6 (17%) were infected with Coxsackievirus group B, 2 (6%) were infected with cytomegalovirus, and 1 (3%) was infected with Epstein-Barr virus.

ENDOCARDITIS

Marantic endocarditis or nonbacterial thrombotic endocarditis is characterized by friable, fibrinous clumps of platelets and red blood cells adherent to the cardiac valves without an inflammatory reaction. It is estimated that this condition occurs in 3% to 5% of AIDS patients. It usually occurs in patients older than 50 years. Marantic endocarditis is known to be associated with malignant neoplasms, hypercoagulable states, and chronic wasting disease. Mitral and aortic valves are commonly involved in HIV-negative patients, but the tricuspid valve is usually involved in AIDS patients. Systemic embolism can occur in up to 42% of patients, but most of these events are clinically silent. Embolization can involve the brain, lung, spleen, kidney, and coronary arteries. Systemic embolization from marantic endocarditis is a rare cause of death in AIDS patients.

Infective endocarditis in patients with AIDS usually occurs in parenteral drug users. Human immunodeficiency virus infection may increase the risk of infective endocarditis among intravenous drug users. Nahass et al studied the causes of infective endocarditis in 34 HIV patients, and they found that Staphylococcus aureus (75%) and Streptococcus viridans (20%) were the major responsible organisms. Other unusual organisms described as case reports were Salmonella, A. fumigatus, and Pseudallescheria boydii. The tricuspid valve is the most commonly affected valve. The affected patients usually present with fever, sweats, weight loss, and coexisting pneumonia and/or meningitis. The presentation and survival of infective endocarditis in patients with and without HIV infection are generally not different; however, in the late stage of HIV-infected patients, significant increased mortality from infective endocarditis has been reported compared with asymptomatic HIV patients.

PULMONARY HYPERTENSION

Human immunodeficiency virus–associated pulmonary hypertension was first described by Kim and Factor in 1987. By 1998, 88 patients with HIV infection were described with this entity. The incidence of HIV-associated pulmonary hypertension is 1 in 200 compared with 1 in 200 000 in the general population.
population. It is more common in male and young patients (mean age, 32 years). The common risk factors are intravenous drug use, homosexual contacts, and hemophilia. The major symptom of this condition is dyspnea. There was no correlation between either a history of opportunistic infections or CD4 cell count and the development of pulmonary hypertension. The mean pulmonary artery systolic pressure was 68 mm Hg. The major causes of death were rightsided heart failure and respiratory failure. Half of the patients died in 1 year. Petitpretz et al performed a prospective study of 20 patients with HIV infection and pulmonary hypertension and compared them with a group of 93 patients with primary pulmonary hypertension who were HIV negative. They found that patients with HIV infection were younger and had a lesser degree of disabilities. Interestingly, mortality between these 2 groups was not different. Plexogenic pulmonary arteriopathy was the most frequent pathologic finding.

The pathogenesis of pulmonary hypertension associated with HIV infection is unclear. Mette et al were unable to demonstrate the presence of HIV in pulmonary endothelial cells by electron microscopy, immunocytochemistry, DNA in situ hybridization, and the polymerase chain reaction technique. This finding supports an indirect mechanism for HIV-associated pulmonary hypertension. Ehrenreich et al demonstrated that HIV-1 envelope glycoprotein (GP-120) stimulated the production of the secretion of endothelin 1 (a potent vasoconstrictor) and tumor necrosis factor α from macrophage. Human immunodeficiency virus–infected alveolar macrophage released tumor necrosis factor α and proteolytic enzymes. Lymphokine can enhance the adherence of the leukocyte to the endothelium and promote endothelial proliferation. Platelet-derived growth factor can stimulate smooth muscle cell and fibroblast proliferation and migration. Humbert et al showed that platelet-derived growth factor expression was increased in patients with HIV-associated pulmonary hypertension. Morse et al found that the incidence of HLA-DR6 and HLA-DR52 was increased in 10 HIV patients with primary pulmonary hypertension compared with matched control subjects. Human immunodeficiency virus–associated pulmonary hypertension is a diagnosis of exclusion. Other causes of pulmonary hypertension include tcalc granuloma, especially in intravenous drug abusers, portal hypertension, thromboembolism, and an airway disease.

**CARDIAC NEOPLASM AND HIV**

Two types of malignant neoplasms affecting the heart have been described in patients with HIV infection: Kaposi sarcoma and malignant lymphoma.

**Kaposi Sarcoma**

In 1983, Autran et al first described Kaposi sarcoma of the heart in an HIV patient. The incidence of Kaposi sarcoma involving the heart ranged from 12% to 28% in retrospective autopsy findings. Most (90%) of the autopsies were performed on homosexual or bisexual patients. Cardiac involvement with Kaposi sarcoma in an HIV-infected patient usually occurs as a part of disseminated Kaposi sarcoma. Acquired immunodeficiency syndrome–related metastatic Kaposi sarcoma involves either the visceral layer of serous pericardium or the subepicardial fat. There is a predilection of Kaposi sarcoma to involve the subepicardial adipose tissue adjacent to a major coronary artery with or without involvement of the adventitia of the ascending aorta or pulmonary trunk. Pericardial and myocardial involvement have also been reported. Chyu et al demonstrated premortem detection of cardiac Kaposi sarcoma by transthoracic echocardiography, which revealed pericardial tamponade and a mobile multilobular mass at the apex protruding into the pericardial space. Clinical cardiac findings are obscure; most of the cases are found at autopsy. Fatal cardiac tamponade and pericardial constriction have been reported. Vijay et al reported 5 cases of Kaposi sarcoma of the visceral layer of serous pericardium or pericardium causing fatal tamponade in the patients with AIDS. Percardicentesis was performed, resulting in a transient improvement in vital signs but with subsequent deterioration and death within a variable period ranging from 5 hours to a few days. The diagnosis of pericardial Kaposi sarcoma was delayed until autopsy. All were noted to have a tense pericardial sac with dark bloody fluid, presumably as a result of the pericardicentesis needle penetrating the Kaposi sarcoma lesions. Percardicentesis not only has no diagnostic role but it is also a high-risk procedure in this group of patients. In patients with AIDS in whom the clinician has a high index of suspicion of Kaposi sarcoma pericardial effusion, a pericardial window should be the procedure of choice for providing decompression and establishing the pathologic diagnosis.

**Malignant Lymphoma**

In 1985, the Centers for Disease Control and Prevention recognized the linkage between intermediate- and high-grade lymphoma and HIV seropositivity and included this in the diagnostic criteria for AIDS. Lymphoma is the second most common tumor that involves the heart. Cardiac involvement with non-Hodgkin lymphoma, usually derived from B cells, is typically high grade and is often disseminated early in patients with AIDS. Disseminated cardiac lymphoma is more common than primary cardiac lymphoma. It has been reported to account for 15% of all cardiac and pericardial metastases in non-AIDS series. Primary cardiac lymphoma is extremely rare. Patients may present with intractable congestive heart failure, pericardial effusion, cardiac arrhythmia, or cardiac tamponade. Patients usually have nonspecific symptoms, but rapid progression of cardiac dysfunction can occur after these symptoms. The most common gross appearance is nodular or polyloid masses predominantly involving the pericardium, with variable myocardial infiltration. Histologically, these are diffuse, aggressive lymphomas, usu-
ally of small noncleaved or immunoblastic types.59 Patients with mechanical obstruction may benefit from surgical resection.60 The prognosis of patients with HIV-associated cardiac lymphoma is generally poor, although clinical remission has been observed with combination chemotherapy.60

CORONARY ARTERY DISEASE

Coronary artery disease has been reported in a patient with HIV infection81,82 at autopsy. Eccentric atherosclerosis or fibrosis of the tunica media of the coronary artery was found at autopsy.83 Sclerohyalinosis of the smaller arteries and myocardial interstitial fibrosis lesions were also found.84 The cause of these lesions is uncertain. Coronary artery disease in HIV-positive patients may be due to atherogenesis as a result of virus-infected monocytes-macrophages, possibly through altered adhesion93 or due to angiitis.82,84 Atherosclerosis and atherothrombosis from dyslipoproteinaemia caused by highly active antiretroviral therapy, especially protease inhibitors, have been reported.85

DRUG-INDUCED CARDIOTOXICITY

Patients with HIV are exposed to many medications to treat conditions related to HIV diseases, such as cancer and opportunistic infections. Some of these medications may have cardiovascular toxicities. Dilated cardiomyopathy has been reported in a young male patient treated with amphotericin B.90 In this patient, cardiac function returned to normal after the medication had been discontinued for 6 months.97 Bradycardia was described in children treated with amphotericin B. The incidence was 6.7% in the patients who received amphotericin B and usually occurred between days 3 and 7 after the start of therapy.98 Hypertension was found in 2 patients treated with amphotericin B, and the mechanism of this adverse effect was unclear.99 Doxorubicin cardiomyopathy has been well described and occurred with a total dose of 400 mg/m² or more.100 The prevalence of hypertension associated with erythropoietin therapy is 47%, and the mechanism of this adverse effect may be related to an increase in hematocrit and blood viscosity.101 Reversible cardiomyopathy has been described in HIV patients treated with foscarnet sodium for cytomegalovirus esophagitis.102 Cohen et al103 described 2 patients who developed ventricular tachycardia during an intravenous infusion of ganciclovir. Sonnenblick and Rosin104 reviewed 44 cases of interferon-induced cardiodotoxicity. Arrhythmia was the most common manifestation of cardiotoxicity (25 patients). Other cardiotoxicities included myocardial infarction or ischemia (9 patients), cardiomyopathy (5 patients), sudden death (2 patients), AV block (2 patients), and congestive heart failure (1 patient). Cardiac adverse effects from interferon were not associated with the dosage or the duration of treatment and were reversible in most patients.104 QT prolongation has been reported in patients treated with pentamidine,105,106 pyrimethamine,107 and the combination drug trimethoprim and sulfamethoxazole.108 Cardiac dysfunction has been found in adults or children treated with zidovudine. Zidovudine inhibits retroviral replication and interferes with the action of reverse transcriptase of HIV.109,110 Diffuse destruction of cardiac mitochondrial ultrastructures and inhibition of mitochondrial DNA replication may be responsible for zidovudine-induced cardiomyopathy (Table 2).111

CONCLUSIONS

Cardiac involvement is commonly seen in AIDS patients, and the pericardium, myocardium, and/or endocardium may be involved in these patients. Pericardial effusion is one of the most common types of cardiac involvement in HIV patients, and its mechanism is unclear but it may be related to infections or neoplasms. Myocarditis, the cause of which is usually difficult to identify, may be responsible for myocardial dysfunction. Opportunistic infections have been reported to be a cause of myocarditis, including the HIV itself. Dilated cardiomyopathy is usually found in the late stage of HIV infection, and myocarditis may be the triggering causative factor. Nonbacterial thrombotic endocarditis and infective endocarditis have been described in AIDS patients, both of which can cause significant morbidity in these patients. Human immunodeficiency virus-related pulmonary hypertension is a diagnosis of exclusion, and symptoms and signs may mimic other pulmonary conditions in AIDS patients. Cardiac Kaposi sarcoma and cardiac lymphoma are the frequently encountered malignant neoplasms in AIDS patients, and the prognosis is grave in patients with these conditions. Coronary artery disease has previously been documented and may be related to highly

Table 2. Cardiotoxicity of Medications Used in HIV Patients

<table>
<thead>
<tr>
<th>Medications</th>
<th>Treatment</th>
<th>Cardiovascular Adverse Effects</th>
</tr>
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<tbody>
<tr>
<td>Amphotericin B</td>
<td>Antifungal</td>
<td>Dilated cardiomyopathy, hypertension, and bradycardia</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Kaposi sarcoma</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Anemia</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Foscarnet sodium</td>
<td>CMV</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>CMV</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>Interferon alfa</td>
<td>Antineoplastic, antiviral, and immunomodulator</td>
<td>Arrhythmia, myocardial infarction or ischemia, cardiomyopathy, sudden death, AV block, and congestive heart failure</td>
</tr>
<tr>
<td>Pentamidine</td>
<td><em>Pneumocystis carinii</em></td>
<td>QT prolongation and Torsades de pointes</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>Toxoplasmosis</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td><em>P carinii</em></td>
<td>QT prolongation and Torsades de pointes</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Antiretroviral</td>
<td>Myocarditis and dilated cardiomyopathy</td>
</tr>
</tbody>
</table>

* HIV indicates human immunodeficiency virus; CMV, cytomegalovirus.
active antiretroviral therapy. Many cardiovascular adverse effects from medications used in HIV patients have been described. As the survival of HIV patients has improved mainly because of aggressive antiretroviral therapy, it is anticipated that more late complications from this fatal viral infection, including cardiac involvement, will be encountered. Early recognition and prompt treatment are important to prevent significant morbidity from cardiac involvement. Whether this approach will prolong survival in AIDS patients remains to be seen.

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sades de pointes after administration of trimeth-


107. Herskowitz A, Willoughby SB, Baughman KL,

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110. Herskowitz A, Willoughby SB, Baughman KL,

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