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Review

Cardiac Surgery in HIV Patients: State of the Art

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ABSTRACT

The clinical status of HIV infection has changed dramatically with the introduction of combined antiretroviral therapy. Patients with HIV are now living long enough to be susceptible to chronic illnesses, such as coronary disease and nonischemic cardiomyopathy, which can be consequences of the combined antiretroviral therapy treatment itself. Cardiovascular diseases are a major source of morbidity and mortality in HIV-positive patients. Increasingly, such patients might be candidates for the full range of cardiac surgical interventions, including coronary bypass, valve surgery, and heart transplantation. There has been a shift from offering palliative procedures such as pericardial window and balloon valvuloplasty, to more conventional and durable surgical therapies in HIV-positive patients. We herein provide an overview of the contemporary outcomes of cardiac surgery in this complex and unique patient population. We review some of the ethical issues around the selection and surgical care of HIV-positive patients. We also discuss strategies to best protect the surgical treatment team from the risks of HIV transmission. Finally, we highlight the need for involvement of dedicated infectious disease professionals in a multidisciplinary heart team approach, aiming at the comprehensive care of these unique and complex patients.

RÉSUMÉ

Le statut clinique de l'infection par le VIH a évolué de façon spectaculaire avec l'avènement du traitement antirétroviral combiné. Les patients infectés par le VIH ont à présent une espérance de vie assez longue pour pouvoir être atteints de maladies chroniques comme la coronaropathie et la cardiomyopathie non ischémique, qui peuvent être la conséquence du traitement antirétroviral combiné lui-même. Les maladies cardiovasculaires sont une cause majeure de morbidité et de mortalité chez les patients séropositifs pour le VIH. De plus en plus, ces patients pourraient être candidats à l'une des interventions de l'éventail complet des chirurgies cardiaques, y compris le pontage coronarien, la chirurgie valvulaire et la transplantation cardiaque. L'approche consistant à proposer aux patients séropositifs pour le VIH des interventions palliatives comme la fenêtre péricardique et la valvuloplastie par ballonnet a été abandonnée au profit de modalités plus classiques et plus durables. Dans le présent article, nous présentons une vue d'ensemble actualisée des résultats de la chirurgie cardiaque dans cette population de patients complexe et unique. Nous examinons certains des enjeux éthiques entourant la sélection et les soins chirurgicaux des patients vivant avec le VIH. Nous abordons également la question des stratégies visant à protéger au mieux l'équipe d'intervention chirurgicale contre le risque de transmission du VIH. Enfin, nous soulignons la nécessité de privilégier l'approche de l'équipe de cardiologie interdisciplinaire à laquelle seraient intégrés des professionnels spécialistes des maladies infectieuses, avec pour objectif d'offrir tout l'éventail des soins à ces patients uniques et complexes.

Patients with HIV are now living long enough to be susceptible to chronic illnesses, such as coronary disease and nonischemic cardiomyopathy. We provide an overview of the unique considerations and outcomes of revascularization, valvular, and heart failure surgery in HIV-positive patients, and discuss the need for multidisciplinary heart teams for the comprehensive care of this complex patient population.

Introduction: The Current State of HIV Management

The widespread availability and use of combined antiretroviral therapy (cART) has significantly decreased mortality in HIV-positive patients. Such treatments are given earlier in the course of the disease.[1,2] Globally, yearly deaths are down from 1.9 million to 900,000, new infections are down from

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3.4 to 1.8 million per year, and 22 million people are receiving antiretroviral therapy worldwide.[3] The focus of treatment is shifting to postexposure and preexposure prophylaxis. Patients with HIV have seen a remarkable increase in life expectancy, can now often live for decades, and generally enjoy a good quality of life. HIV infection is being reconceptualized as a chronic illness; the total intrinsic mortality from HIV infection has decreased, however cardiovascular mortality has increased in this patient population (Fig. 1, red line).[4,5] For comparison, the proportionate cardiovascular disease mortality continues to decrease in the general population and in patients with inflammatory polyarthropathy but remains responsible for a significant overall burden of deaths (Fig. 1, green and blue lines).

There has been a remarkable increase in life expectancy for patients with HIV in the developed world. A study of 88,504 patients in Europe and North America who started cART between 1996 and 2013 showed marked improvements in life expectancy of HIV-positive subjects.[6] A US study of 24,768 HIV-infected individuals reported an overall improvement in life expectancy at age 20 years to 53 years, narrowing the gap relative to HIV-uninfected individuals to 8 years when receiving cART.[7] Similar results were reported in a matched cohort study of 16 ,532 HIV-positive Swiss patients.[8] Life expectancy at age 20 years in HIV-positive individuals was 55 years in the most recent era; this approached that of the HIV-uninfected population.[9,10] Thus, current life expectancy is estimated to reach the sixth or seventh decade under ideal conditions but this continues to be a moving target and additional positive strides are likely to be observed.

The heart is vulnerable to HIV-related coronary artery disease, opportunistic infections, and drug-related myocardial injury. Patients with HIV have a 4.5-fold excess risk of cardiovascular disease resulting in sudden cardiac death compared with age- and sex-matched controls from the general population.[11] The cardiac pathology seen in HIV patients is shifting to accelerated coronary artery disease and ischemic cardiomyopathy.[12] Some of the cardiovascular risk is due to traditional risk factors in an aging population. There is a greater incidence of traditional cardiovascular risk factors including smoking and dyslipidemia in the HIV-positive population.[4] However, a prospective cohort study of more than 82,000 patients in the Veterans Aging Cohort Study virtual cohort revealed that patients with HIV infection have a 50% increased risk of acute myocardial infarction beyond that explained by traditional risk factors (hazard ratio, 1.48; 95% confidence interval [CI], 1.27-1.72).[12] The exact mechanism of HIV-related coronary disease is unknown, but has been hypothesized to relate to chronic inflammation, a hypercoagulable state, dyslipidemia, endothelial dysfunction, metabolic syndrome, and others.[13,14] People with HIV are dyslipidemic, likely as a result of traditional risk factors, but also from abnormal lipid metabolism due to the HIV infection itself, as well as from the effects of the cART treatment on lipid metabolism.[15] Current-generation drugs are less cardiotoxic, but still carry adverse cardiovascular effects.[16,17]

Primary and secondary cardiovascular prevention in the HIV-positive population is an active area of clinical investigation. A search of ClinicalTrials.gov revealed > 100 clinical trials and studies investigating cardiovascular disease treatment in patients with HIV. There are ongoing randomized trials to determine the role of statins (**R**andomized Trial to **P**revent Vascular Events in HI**V** [REPRIEVE], ClinicalTrials.gov Identifier: NCT02344290), mineralocorticoid receptor antagonist (**M**ineralocorticoid **R**eceptor **A**ntagonism for **C**ardiovascu**l**ar H**e**alth in **HIV** [MIRACLE HIV], ClinicalTrials.gov Identifier: NCT02740179), and Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors (Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection [EPIC-HIV Study], ClinicalTrials.gov Identifier: NCT03207945) in this patient population.

Herein, we provide a focused overview of the cardiac surgical management in this unique and high-risk patient population. We highlight surgical candidacy and contemporary ethical issues, as well as strategies for the protection of surgical personnel from HIV exposure (Table 1).

Medical and Ethical Considerations

For the most part, HIV-positive patients should be considered candidates for life-saving cardiac surgery. However, a few exceptions apply when patients might be turned down for surgery, because of high surgical risk or poor long-term prognosis. Patients who are not adherent with cART, which is critical for achieving immunocompetence, have a poorer prognosis from HIV infection itself.

Patients with AIDS including seropositive HIV, low cluster of differentiation-4 T-cell (CD4+) count, recent opportunistic infection(s), and secondary cancers have limited long-term survival. There are limited data on cardiac surgery in patients with symptomatic AIDS because many such patients are not offered surgery and case series of HIV patients exclude this high-risk cohort.[18] Furthermore, the safe CD4+ count for cardiac surgery is controversial. Successful surgery has been reported in patients with CD4+ counts of < 200 cells/mm^3.[19] We performed emergent valve surgery for infective endocarditis on a patient with a CD4+ count of < 10 cells/mm^3 with no adverse perioperative events (unpublished observations).

Patients who acquired HIV via injection drugs or with a history of drug addiction have a dismal short- and mid-term survival.[20] In this regard, a series of 31 HIV-infected patients reported the highest mortality in patients who underwent valvular surgery for infective endocarditis-associated with injection drug use, in contrast to no mortality in patients who underwent coronary revascularization.[21] Chong et al.[22] also reported a 45% mid-term mortality in 22 HIV-infected patients who underwent valve replacement for intravenous drug use-related infective endocarditis. Notably, most of the patients died of complications related to drug addiction.

There are several potential ethical issues related to HIV in cardiac surgery that deserve brief mention:

(1) *What are the regulations regarding blood-borne pathogen status of surgeons?*

This varies according to jurisdiction. According to the College of Physicians and Surgeons of Ontario, physicians must be tested for HIV before performing or assisting in exposure-prone procedures and every 3 years thereafter.[23] Similar regulations exist in British Columbia but routine testing for HIV among physicians is not supported by the College of Physicians and Surgeons of Quebec.[24,25]

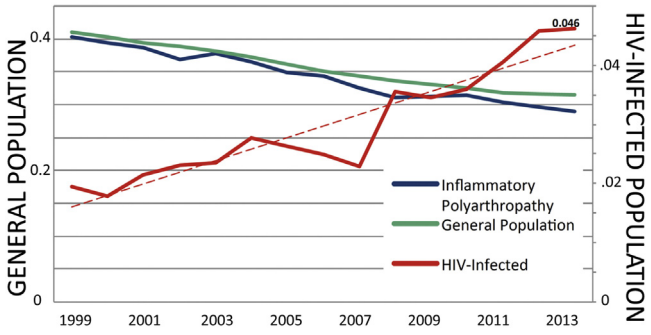

Figure 1. Burden of mortality for cardiovascular deaths in the Centers for Disease Control and Prevention Wide-Ranging Online Database (United States; 1999-2013): overall increase in the HIV-infected (**red**, **right Y-axis**) vs a decrease in the general (**green**, **left Y-axis**) and inflammatory polyarthropathy populations (**blue**, **left Y-axis**). Reproduced from Feinstein et al.[5] with permission from Elsevier.

(2) *Must HIV-positive surgeons disclose their HIV status to patients?*

The Public Health Agency of Canada suggests that health care workers who perform exposure-prone procedures have an obligation to report their status to their regulatory body. The Public Health Agency of Canada has published guidance on the management of health care workers infected with a blood-borne pathogen. They have a consultation mechanism that includes referral to an expert panel.[26] In most cases, because of the extremely small risk of transmission, patients do not need to be notified of the health status of an HIV-infected health care worker.

(3) *Must surgeons report HIV-positive status of a patient?*

Yes, HIV infection is reportable by law to the public health authorities in all provinces and territories in Canada.[27]

Cardiac Surgery Can Be Performed Safely in HIV Patients

For any given patient, cardiac surgery can be accompanied by significant surgical and metabolic stresses. The use of cardiopulmonary bypass itself is associated with a systemic inflammatory response syndrome, coagulopathy, micro-embolism, and other insults. There were some early concerns regarding the effect of extracorporeal circulation on weakening the immune status of patients with HIV.[28] However, this has not been borne out in the clinical experience. The surgical mortality in select patients with HIV who undergo cardiac surgery is comparable with that of a non-HIV cohort (Table 2). Unfortunately, no comparable Canadian data on outcomes of surgery in HIV patients are available.

Table 1. Key considerations for cardiac surgery in the HIV population

Estimated life expectancy
Might consider nonsurgical intervention
Might influence valve or graft selection
Risk of perioperative opportunistic infection
Will use of mechanical circulatory support and/or transplantation for post-cardiotomy cardiogenic shock be considered?
Modifications to immunosuppressive therapy after transplantation
Safety of operating room staff
Protocol modifications to minimize risk of HIV transmission to surgical staff
Might consider personnel changes (eg, no trainees)

Two studies of the Nationwide Inpatient Sample have reported a 2- to 2.5-fold increase in the frequency of heart surgery in patients with HIV.[29,30] Polanco et al.[30] reported that HIV status was not an independent predictor of surgical mortality (adjusted odds ratio [OR], 0.88; 95% CI, 0.64-1.2; $P = 0.4$). The independent predictors of surgical mortality in HIV-positive patients were age, renal failure, and valve surgery, which are similar to risk factors in the non-HIV population. Robich et al.[29] also showed that HIV infection was not an independent risk factor for mortality in a propensity-matched analysis (OR, 0.8; 95% CI, 0.74-1.30). Again, the independent risk factors for mortality in HIV-positive patients included metastatic cancer (in patients undergoing pericardial drainage), coagulopathy, and complexity of surgery. Thus, the immunological and physiological reserve of HIV-positive patients appear to be comparable with those without HIV, and HIV status alone should not dictate candidacy for cardiac surgery. In the Society for Thoracic Surgeon's Risk Score, HIV patients with reduced CD4+ count might be considered to have "immunocompromised" status as a risk factor for surgical mortality.[31]

Coronary Bypass in People With HIV Infection

It remains unclear whether HIV status should tilt the pendulum of coronary revascularization toward percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). HIV-positive patients do have a proinflammatory milieu with increased platelet reactivity.[32] Thus far, short-term outcomes of PCI with drug-eluting stents in HIV patients seem comparable with that of the general population.[33] For coronary bypass surgery, again data from the Nationwide Inpatient Sample Database showed that HIV status was not associated with increased risk of cardiac surgical mortality.[29,30] In fact, isolated CABG in HIV-positive patients was shown to have a lower surgical mortality, compared with non-HIV patients (1.5% vs 2.4%; $P = 0.03$), likely reflective of the selection bias in this population. Trachiotis et al.[34] reported their experience with cardiac surgery in 37 HIV-infected patients, in whom 73% of cases were CABG. In the CABG group, there were no surgical mortalities, mediastinitis in 1 (2.7%), bleeding in 1 (2.7%), prolonged ventilation in 1 (2.7%), and readmission in 9 patients (33%). At 5 years, there was a 70% freedom from death, angina, or repeat revascularization. A large multicentre case control study also reported comparable surgical outcomes between HIV-positive and -negative patients who underwent CABG.[21]

Because of these results, patients with HIV should be considered for surgical revascularization. Indeed, CABG is the most common surgery for patients with HIV (Fig. 2).[29] A cohort study of the National Inpatient Sample (United States) reported rates of cardiac procedures among 1,091,759 patients, including 3783 with HIV (0.4%).[18] In a multivariable analysis, there was no difference in catheterization (OR, 0.93; 95% CI, 0.81-1.07), PCI (OR, 1.06; 95% CI, 0.93-1.21), and CABG rates (OR, 0.88; 95% CI, 0.72-1.06) in patients with HIV, compared with those without HIV. However,

Table 2. Surgical mortality for cardiac surgery in the HIV population

Reference	Year	HIV, n	Procedure	Surgical mortality
Trachiotis et al.[34]	1994-2000	37	CABG/valve	2.7%
Robich et al.[29]	1998-2009	9771	CABG/valve/aortic/other	7.2% vs 4.3% for non-HIV ($P < 0.001$)
Polanco et al.[30]	2000-2010	1239	CABG/valve	2.6% vs 3.3% for non-HIV ($P = 0.003$)
Boccara et al.[32]	1997-2005	27	CABG	0% vs 0% for non-HIV

CABG, coronary artery bypass grafting.

those with symptomatic AIDS were less likely to undergo intervention for acute coronary syndrome. Thus, CABG can be performed safely and with the expectation of a good short- and mid-term outcome, in select HIV-positive patients.

Valve Surgery in People With HIV Infection

There has been a shift from valve surgery because of infection from opportunistic infections, to cardiac surgery predominantly for coronary revascularization. Between 2000 and 2010, of all HIV-positive patients who underwent cardiac surgery, the proportion who underwent valve surgery for endocarditis decreased from 32% to 8%.[30] One major exception remains patients who inject intravenous drugs, in whom infective endocarditis is still prevalent. Such patients frequently require repeat surgery and have a poor short- and mid-term survival, primarily because of complications related to their drug addiction.[20,22]

As patients with HIV live longer, they are at risk of developing aortic stenosis and mitral regurgitation like the non-HIV population. The choice of the valve prosthesis (ie, bioprosthetic or mechanical), should be made on the basis of the overall prognosis of the patient and the risk of oral anticoagulation. As mentioned, life expectancy for patients aged 20 years with HIV receiving cART is 50-60 years. Finally, patients who are not candidates for conventional aortic valve replacement might be considered for transcatheter aortic valve replacement.[35]

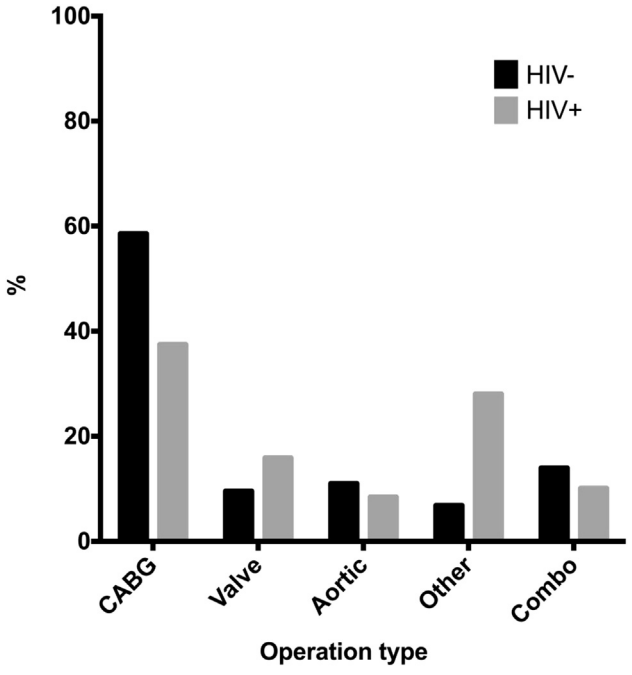

Figure 2. Distribution of 5,621,817 cardiac surgical procedures in the Nationwide Inpatient Sample (1998-2009) including 9771 (0.17%) HIV-positive patients. CABG, coronary artery bypass graft; Combo, combined surgery. Reproduced from Robich et al.[29] with permission from Elsevier.

Heart Failure Surgery in People With HIV Infection

Patients with HIV are susceptible to ischemic and non-ischemic cardiomyopathy.[36,37] The latter can result from direct HIV effects, cytokine activation, immune system dysregulation, myocarditis by opportunistic pathogens, side effects of cART, or a combination thereof.[38] These patients might be candidates for guideline-directed therapy, including mechanical circulatory support and heart transplantation.

There are several reports of short-term success with left ventricular assist devices in the HIV patient population, as a destination and as a bridge to transplant.[39-41] However, clinical reports of heart transplantation in HIV-infected patients are case series or single-centre reports, in which short-term outcomes are comparable with the non-HIV patient population.[26,41] The first reported case of an HIV-positive patient treated with heart transplantation for advanced heart failure was in 2003.[42]

The Texas Heart Institute's inclusion criteria for heart transplantation in HIV-positive patients are: (1) HIV-negative serostatus; (2) CD4+ count of 450-2500 cells/μL for 6 months to 1 year; (3) adherence to cART for 1 year; and (4) undetectable HIV viral load.[43] The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation supports the use of this modality in selected HIV-positive patients, provided that they have: (1) no history of HIV-related infections; (2) adherence to cART; (3) undetectable HIV viral load; and (4) CD4+ count > 4200 cells/μL.[44] Patients with a history of central nervous system lymphoma or Kaposi sarcoma should not be considered candidates for heart transplantation. Despite this recent shift in guidelines, some transplant centres still consider HIV infection to be a contraindication for transplantation.[45]

The management of antiviral and immunosuppressive therapies after heart transplantation should be tailored and carefully managed by an experienced multidisciplinary transplant and HIV-specialist team.

Multidisciplinary Team

In cardiovascular medicine, the multidisciplinary team might involve a cardiologist, surgeon, anaesthesiologist, intensivist, primary care physician, nurse, physiotherapist and occupational therapists, social worker, and other specialists as needed. The care of patients with HIV should also involve a

dedicated infectious disease specialist, or "HIV specialist." This is especially true in the case of heart transplantation in HIV-positive patients, which involves tailored immunosuppressive and antiretroviral therapy.

Safety for Operative Room Staff

Operating on any patient places the risk of biohazardous transmission to health care staff. Despite the highest standards of infection control, including universal safety precautions, there remains a risk of needle-stick injury to the operating room staff. Of 37 cardiac surgical procedures in HIV-infected patients, there were 6 "needlestick" injuries reported, requiring antiretroviral prophylaxis in 5 medical personnel.[20] There was no seroconversion. A systematic review estimated a per-event risk of 23 of 10,000 cases (0.23% risk) of HIV transmission from a needle-stick injury.[46]

Surgery on patients with HIV can be performed safely, with minimal risk to surgical staff, by the routine use of sterile technique and universal precautions, as well as with some additional precautions. First and foremost, it can be proposed that such cases are not appropriate for surgical teaching. Trainees should be given the option of not scrubbing in because of the greater risk of needle-stick injury. We also advocate for experienced surgical and nursing personnel to scrub in for such cases. Last, we favour additional manoeuvres to minimize the potential for needle-stick injury, including the passing of any sharp instrument in a sterile container, which is transferred as needed from surgeons to the scrub nurse, and vice-versa. We also strongly recommend "double-gloving" for all cases, a practice that has been shown in multiple randomized controlled trials to reduce surgeon percutaneous blood exposure.[47]

In patients with seronegative HIV status, the blood concentration of viral particles is low or nil. However, if a needle-stick injury was to occur, we recommend an immediate Betadine rinse of the affected area and the use of appropriate post-exposure prophylaxis.[48] Local practices vary with regard to post-exposure prophylaxis. The British Columbia Centre for Excellence in HIV/AIDS recommends a 28-day course of tenofovir DF 300 mg orally (PO) once daily, lamivudine 150 mg PO twice daily, and raltegravir 400 mg PO twice daily to start within 72 hours of exposure but preferably within 2 hours.[49]

Conclusion

The prognosis of patients with HIV has improved dramatically over the past 2 decades. People with HIV are susceptible to cardiovascular diseases including coronary, valvular, and myocardial diseases. In most cases, they are candidates for the full range of cardiac surgical care and the surgical and mid-term outcomes compare favourably with that of the overall population. The risk of intraoperative transmission of HIV from health care worker to patient and vice versa is minuscule. Nevertheless, there are a few strategies that the surgical team can implement to ensure the safety of all. Finally, there is a need for a multidisciplinary heart team for optimal care of this unique and complex patient population.

Disclosures

The authors have no conflicts of interest to disclose.

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