Translating Chagasic dilating cardiomyopathy to surgical therapies: An under published global challenge

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Abstract
Chagas disease is a neglected parasitic anthropozoonosis of the Americas linked to social deprivation with no hope of eradication in the future. Having been the most common non-ischemic cause of dilating cardiomyopathy in Latin America, it now spreads beyond the geographical boundaries of its vector via imported and autochthonous transmission. We review the evidence on surgery in Chagasic heart failure and offer a brief narrative on the main aspects of translational management. There is very limited literature on surgery for Chagasic heart failure, especially assist devices and transplantation. This may be attributed to the often unsurmountable economic burden of this single-system parasymphatholytic heart failure to young sufferers who commonly have very limited access to the aforementioned procedures. Chagasic heart failure offers a so far neglected translational model of parasymphatholytic non-ischemic cardiac failure.

Keywords
Chagas disease, global health, tropical disease, tropical surgery, American trypanosomiasis

Introduction
Trypanosomes are flagellate protozoa responsible for a number of parasitic infections in humans. American trypanosomiasis, or more commonly Chagas disease (CD), named after Dr Carlos Justiniano Ribeiro das Chagas (1879–1934) is recognized by the World Health Organization (WHO) as a “neglected tropical diseases” (NTDs).¹ Chagas cardiovascular disease (CCVD), or chronic Chagas heart disease (cChHD), is rife in Central and South America with no sight of eradication on the horizon.¹–³ It is the most common non-ischemic cause of dilating cardiomyopathy (DCM) and resultant Chagasic heart failure (ChHF) in Latin America.⁴ ChHF is also becoming a problem in Texas via imported and autochthonous transmission.³ The parasite can often be reactivated.⁶

Increased understanding and awareness of the disease, especially its parasymphatholytic cardiac and extracardiac manifestations, will be of relevance to cardiovascular clinicians in future.⁷–¹² Given increasing exposure to the parasite that the developing world can expect to see,⁹ With the global repercussions of ChHF in mind,¹¹ we review what is published on surgery for ChHF. Orthotopic cardiac transplantation and ventricular assist are often unsurmountable financial burdens in low- and middle-income countries (LMICs).

Review of the literature
We reviewed Ovid MEDLINE databases for relevant literature, in English language, from 1946 to 1 July 2017. The search was led by Mr Folu Ojutalayo, Library Manager and Liaison Librarian Royal Brompton Campus Library, Imperial College London (Search strategy in Table 1).

Epidemiology
Trypanosoma cruzi, the flagellate protozoal causative agent of American trypanosomiasis (CD), is widespread in Central and South America and the disease is endemic in approximately

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Table 1. Search strategy.

| Search term                              | Count  |
|------------------------------------------|--------|
| Chagas disease {No Related Terms}       | 11,248 |
| Trypanosomiasis {No Related Terms}      | 8353   |
| Preoperative cardiovascular practice     | 9330   |
| Clinical AND Medical Management {No Related Terms} | 10,233 |
| Clinical Presentation {No Related Terms} | 7021   |
| Parasite {No Related Terms}             | 8937   |
| Trypanosomiasis America.mp.              | 0      |
| Chagas Disease/ (10,446)                 |        |
| 1 or 2 or 3 (39,458)                    |        |
| 4 or 5 or 6 (83,185)                    |        |
| 8 and 9 and 10 (14)                     |        |
| 1 or 4 (5497)                           |        |
| 1 or 4 or 6 (7560)                      |        |
| 3 or 5 or 8 (111,636)                   |        |
| 13 and 14 (232)                         |        |

21 countries. It is estimated that approximately 8 million people living in the Western hemisphere are infected with *T. cruzi* and that 20%–30% of those infected will subsequently develop symptomatic CD. The WHO estimates that 120 million individuals worldwide are at risk of infection.

*T. cruzi* displays a high degree of genetic variability and can be divided into six specific discrete typing units (DTUs), termed TcI to TcVI. *T. cruzi* DTUs may be linked to different clinical presentations of CD. For example, in a longitudinal study conducted by Burgos et al., a strong correlation between the presence of *T. cruzi* 1 and cardiac damage was observed. In endemic areas, the most common route of transmission of *T. cruzi* is via vector-borne transmission (by triatomine bugs of the genera *Triatoma*, *Panstrongylus*, and *Rhodnius* (Order Hemiptera; Family Reduviidae)), followed by transfusion of contaminated human blood. Vector-borne transmission of the parasite is restricted geographically to countries where triatomine bug vectors are located, ranging from South America to Mexico, with rare cases reported in southern USA. Infection occurs as a result of human contact with contaminated triatomine feces containing the infective stage of *T. cruzi*, metacyclic trypomastigotes. The parasite may then infect a host via the insect bite wound, existing broken skin/wounds or through mucosal membranes such as the conjunctiva. While vector-borne transmission is the most common route of infection, CD may also be transmitted by blood transfusion, organ transplantation, congenital infection, and oral transmission by ingestion of contaminated food or liquid. In urban and non-endemic areas, blood transfusion and congenital transmission are the most common routes of infection.

A review of patterns of *T. cruzi* transmission into non-endemic countries suggested that recent trends in global migration from rural to urban areas, and from endemic to non-endemic countries, have increased the threat of spreading CD on a global level. It was estimated that there are now more than 26 million Latin American immigrants living in Europe, the United States, Canada, Japan, and Australia, which increases the risk of CD spreading to these non-endemic countries. In a most recent study of pooled sero-prevalence data, an overall prevalence of *T. cruzi* in Europe of 4.2% was observed. Triatomine vectors existing in domestic lifecycles can commonly be found in mud walls and thatched roofs of poor-quality housing in rural areas. Because of this, CD is typically linked to socioeconomic status, and the rural poor are those that are most at risk.

We have previously discussed the spectrum of clinical Chagas. We additionally consider the megaesophagus seen mostly in West of Andes Chagas as an important surgical subpathology. It is important to consider Chagas as a systemic neuropathic infection, with multiple manifestations, and as such plan the cardiovascular management.

Medical management

We found ample literature on the medical management of the infection, but little in the cardiac manifestations. The treatment of heart failure in the poor can be a fiscal and social problem, given that heart failure is a chronically morbid condition requiring frequent hospitalizations and change of expensive therapies, culminating to surgery.

Normal interventions such as angiotensin-converting enzyme (ACE) inhibitors or beta-adrenergic blockers may not be well tolerated, thus amiodarone may be suitable for patients with ventricular tachycardia. Alternative solutions include pacemaker placement until cardiac transplant can be performed.

Surgical management

We have not found adequate publications to cover surgery for ChHF. The geographically and historically pertinent procedure, the partial ventriculectomy popularized by Dr Batista for young patients with mostly Chagasic end-stage heart failure, is now not discussed further. It follows that the surgical options are mechanical support and orthotopic heart transplantation (OHT). The paucity of Chagas-specific publications on such surgery may unveil the financial constraints that preclude access of the sufferers to surgical care.

Recipient immunosuppression and reactivation

The immunosuppression required for OHT raises the complex issue of reactivation of *Trypanosoma* in the recipient. It is important to recognize in patients who have underlying CD that disease reactivation can invoke a fever and be mistaken for organ rejection. We found no guidelines on the matter, and it would be of research interest to explore the matter. It is safe to mention that the standard immunosuppression protocols after OHT would not specifically reduce the immunity against parasites.
Limitations

The main objective of our overview was to identify gaps in knowledge relating to surgical approach to ChHF. However, as with any narrative review, our work is subject to selection bias since we had no predefined quantitative research question or prespecified search strategy protocol to assess methodological quality.

Conclusion

Trends in globalization, and climate change, demand that greater attention be paid to the control and management of CD on a global scale. We confirmed that surgery for ChHF is “under published” in the periodicals. The existing literature focuses on chemotherapy and prevention. Patients included in the identified literature were typically young and mostly from LMICs. DCM-ChHF, which manifests in up to 30% of patients when chemotherapy fails, presents fiscal and clinical challenges to the cardiovascular anesthetists, the cardiovascular surgeons, and the cardiovascular intensivists. ChHF offers a so far neglected translational model of parasymphatholytic rhythm-driven (early right bundle branch block (RBBB), left anterior fascicular block (LAFB), or other less common dysrhythmias), and eventually non-ischemic cardiac failure, with occasional pulmonary hypertension. Trypanostatic pharmacology is evolving and is intertwined with intensive care, new diagnostics, and changing epidemiology, as the disease knows no geographical barriers. We could all translate any lessons thus learned to global perioperative healthcare.

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