*Review Paper*

**SAGE Open Medicine**

SAGE Open Medicine
Volume 7: 1–4

DOI: 10.1177/2050312119895927
journals.sagepub.com/home/smo
SAGE

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

**Zoe C Groom[1], Vasileios Zochios[2,3] and Aristotle D Protopapas[4]**

**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

Date received: 5 August 2019; accepted: 27 November 2019

## 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 Americas with no sighting 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.[5] 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,[7–15] 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 an unsurmountable financial burden 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

[1]Costello Medical Consulting Limited, Cambridge, UK
[2]Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, Centre of Translational Inflammation Research, University of Birmingham, West Midlands Deanery, Birmingham, UK
[3]Department of Anaesthesia and Intensive Care Medicine, Glenfield Hospital, University Hospitals of Leicester National Health Service Trust, Leicester, UK
[4]Imperial College London, London, UK

**Corresponding author:**
Aristotle D Protopapas, Imperial College London, London SW7 2AZ, UK.
Email: ap1902@ic.ac.uk

**Table 1.** Search strategy.

| |
|---|
| 1. Chagas disease {No Related Terms} (11,248) |
| 2. Trypanosomiasis {No Related Terms} (8353) |
| 3. Preoperative cardiovascular practice {No Related Terms} (9330) |
| 4. Clinical AND Medical Management {No Related Terms} (10,233) |
| 5. Clinical Presentation {No Related Terms} (7021) |
| 6. Parasite {No Related Terms} (8937) |
| 7. Trypanosomiasis America.mp. (0) |
| 8. Chagas Disease/ (10,446) |
| 9. 1 or 2 or 3 (39,458) |
| 10. 4 or 5 or 6 (83,185) |
| 11. 8 and 9 and 10 (14) |
| 12. 1 or 4 (5497) |
| 13. 1 or 4 or 6 (7560) |
| 14. 3 or 5 or 8 (111,636) |
| 15. 13 and 14 (232) |

21 countries.[1] 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.,[2] a strong correlation between the presence of *T. cruzi* I 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.[4,5] 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.[10] 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 seroprevalence data, an overall prevalence of *T. cruzi* in Europe of 4.2% was observed.[16] 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.[1] We additionally consider the megaesophagus seen mostly in West of Andes Chagas as an important surgical subpathology.[14] 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,[1,7,8,13,17] 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.[18]

## Surgical management

We have not found adequate publications to cover surgery for ChHF.[1] 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.[2,6] It is important to recognize in patients who have underlying CD that disease reactivation can invoke a fever and be mistaken for organ rejection.[19] 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,[13] presents fiscal and clinical challenges to the cardiovascular anesthetists, the cardiovascular surgeons,[14] 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[15,20]), and eventually non-ischemic cardiac failure, with occasional pulmonary hypertension.[21] Trypanostatic pharmacology[22,23] is evolving and is intertwined with intensive care, new diagnostics, and changing epidemiology,[24–26] as the disease knows no geographical barriers.[27] We could all translate any lessons thus learned to global perioperative healthcare.

### Acknowledgements

The authors thank Mr Folu Ojutalayo, Library Manager and Liaison Librarian Royal Brompton Campus Library, Imperial College London, for his invaluable expert contribution.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: V.Z. is supported by an Academic Clinical Fellowship from the National Institute for Health Research (ACF-2016-09-011).

### ORCID iD

Aristotle D Protopapas https://orcid.org/0000-0002-7575-3221

### References

1. Groom ZC, Protopapas AD and Zochios V. Tropical diseases of the myocardium: a review. *Int J Gen Med* 2017; 10: 101–111.
2. Burgos JM, Diez M, Vigliano C, et al. Molecular identification of *Trypanosoma cruzi* discrete typing units in end-stage chronic Chagas heart disease and reactivation after heart transplantation. *Clin Infect Dis* 2010; 51(5): 485–495.
3. Amorim DS, Godoy RA, Manco JC, et al. Effects of acute elevation in blood pressure and of atropine on heart rate in Chagas' disease: a preliminary report. *Circulation* 1968; 38(2): 289–294.
4. Garcia MN, O'Day S, Fisher-Hoch S, et al. One health interactions of Chagas disease vectors, canid hosts, and human residents along the Texas-Mexico border. *PLoS Negl Trop Dis* 2016; 10(11): e0005074.
5. Garcia MN, Woc-Colburn L, Aguilar D, et al. Historical perspectives on the epidemiology of human Chagas disease in Texas and recommendations for enhanced understanding of clinical Chagas disease in the Southern United States. *PLoS Negl Trop Dis* 2015; 9(11): e0003981.
6. Perez CJ, Lymbery AJ and Thompson RC. Reactivation of Chagas disease: implications for global health. *Trends Parasitol* 2015; 31(11): 595–603.
7. Timm BLR, da Silva PB, Batista MM, et al. In vitro and in vivo biological effects of novel arylimidamide derivatives against *Trypanosoma cruzi*. A*ntimicrob Agents Chemother* 2014; 58(7): 3720–3726.
8. Butera JA. Phenotypic screening as a strategic component of drug discovery programs targeting novel antiparasitic and antimycobacterial agents: an editorial. *J Med Chem* 2013; 56(20): 7715–7718.
9. Murthy S, Keystone J and Kissoon N. Infections of the developing world. *Crit Care Clin* 2013; 29: 485–507.
10. Angheben A, Anselmi M, Gobbi F, et al. Chagas disease in Italy: breaking an epidemiological silence. *Euro Surveill* 2011; 16(37): 19969.
11. Coura JR and Vinas PA. Chagas disease: a new worldwide challenge. *Nature* 2010; 465(7301): S6–S7.
12. Biolo A, Ribeiro Al and Clausell N. Chagas cardiomyopathy—where do we stand after a hundred years? *Prog Cardiovasc Dis* 2010; 52: 300–316.
13. Voelker R. A century after Chagas disease discovery, hurdles to tackling the infection remain. *JAMA* 2009; 302(10): 1045–1047.
14. Matsuda NM, Miller SM and Evora PRB. The chronic gastrointestinal manifestations of Chagas disease. *Clinics* 2009; 64(12): 1219–1224.
15. Rodriguez-Angulo H, Marques J, Mendoza I, et al. Differential cytokine profiling in Chagasic patients according to their arrhythmogenic-status. *BMC Infect Dis* 2017; 17(1): 221.
16. Antinori S, Galimberti L, Bianco R, et al. Chagas disease in Europe: a review for the internist in the globalized world. *Eur J Intern Med* 2017; 43: 6–15.
17. Supuran CT. Inhibition of carbonic anhydrase from *Trypanosoma cruzi* for the management of Chagas disease: an underexplored therapeutic opportunity. *Future Med Chem* 2016; 8(3): 311–324.
18. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. *N Engl J Med* 2011; 364: 2527–2534.
19. Toth JE and Domachowske J. Chagas disease: South American trypanosomiasis. In: Domachowske J (ed.) *Introduction to clinical infectious diseases: A problem based approach*. 1st ed. New York: Springer, 2019, pp. 385–391.
20. Traina Hernandez S, Sanchez DR, Dufani J, et al. Prevalence of Chagas disease in a U.S. population of Latin American

immigrants with conduction abnormalities on electrocardiogram. *PLoS Negl Trop Dis* 2017; 11(1): e0005244.
21. Suman AC, Costa Bazan SGZ, Hueb JC, et al. Evaluating respiratory musculature, quality of life, anxiety, and depression among patients with indeterminate chronic Chagas disease and symptoms of pulmonary hypertension. *Rev Soc Bras Med Trop* 2017; 50(2): 194–198.
22. Inaoka DK, Iida M, Hashimoto S, et al. Design and synthesis of potent substrate-based inhibitors of the *Trypanosoma cruzi* dihydroorotate dehydrogenase. *Bioorg Med Chem* 2017; 25(4): 1465–1470.
23. Ogindo CO, Khraiwesh MH, George M Jr, et al. Novel drug design for Chagas disease via targeting *Trypanosoma cruzi* tubulin: homology modeling and binding pocket prediction on *Trypanosoma cruzi* tubulin polymerization inhibition by naphthoquinone derivatives. *Bioorg Med Chem* 2016; 24: 3849–3855.
24. Tanowitz HB and Weiss LM. A new development in *Trypanosoma cruzi* detection. *J Clin Microbiol* 2017; 55(3): 690–692.
25. Balouz V, Aguero F and Buscaglia CA. Chagas disease diagnostic applications: present knowledge and future steps. *Adv Parasitol* 2017; 97: 1–45.
26. Lewis MD and Kelly JM. Putting infection dynamics at the heart of Chagas disease. *Trends Parasitol* 2016; 32(11): 899–911.
27. Luna EJ, Furucho CR, Silva RA, et al. Prevalence of *Trypanosoma cruzi* infection among Bolivian immigrants in the city of Sao Paulo, Brazil. *Mem Inst Oswaldo Cruz* 2017; 112(1): 70–74.