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Biosensors to diagnose Chagas disease: A review

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Abstract: Chagas disease (CD), which mostly affects underprivileged people, has turned into one of Latin America's main public health problems. Prevention of the disease requires early diagnosis, initiation of therapy, and regular blood monitoring of the infected individual. However, the majority of the infections go undiagnosed because of general mild symptoms and lack of access to medical care. Therefore, more affordable and accessible detection technologies capable of providing early diagnosis and parasite load measurements in settings where CD is prevalent are needed to enable enhanced intervention strategies. This review discusses currently available detection technologies and emerging biosensing technologies for a future application to CD. Even if biosensing technologies still require further research efforts to develop portable systems, we arrive to the conclusion that biosensors could improve diagnosis and the patients' treatment follow-up, in terms of rapidity, small sample volume, high integration, ease of use, real-time and low cost detection compared to current conventional technologies.

Keywords: Chagas disease, biosensors, detection technologies, diagnosis, neglected diseases.

1. Introduction

Chagas disease (CD), discovered in 1909 by the Brazilian physician Carlos Chagas (1), nowadays has turned into one of Latin America's main public health problems (2). Based in disability-adjusted life-years as a measure of disease burden, CD figure as the most important parasitic vector-borne illness in the Region of Americas, seven times higher than Malaria and up to three times more than Dengue (3), and yet it is still absent in the agenda of the public health policies and practices of many endemic countries (4, 5). More generally, ranks fourth in mortality and eighth in morbidity

29 among world neglected tropical diseases (6), and is estimated that between eight and eleven
30 million people are infected, while 100 million are at risk of acquiring the disease; the main cause
31 being to live in proximity with disease vectors (7). CD is caused by the parasitic presence of the
32 *Trypanosoma cruzi* in the organism, which is mainly transmitted by contamination with infected
33 feces of blood-sucking triatomine vectors during a human blood meal. Nevertheless, it can also be
34 transmitted through blood transfusions, organ transplants, infected mothers to their unborn
35 children and ingestion of contaminated food (i. e. Oral transmission; WHO, 2002). Although disease
36 progression can be associated with the mechanism of infection, with oral transmission causing the
37 most severe outbreaks (9), people living at risk regions are susceptible to polyparasitism (i.e.
38 Coinfections and superinfections with different strains of *T. cruzi*), with unknown effects in the
39 variability of the disease progression and response to treatments (10).

40 CD mostly affects underprivileged people and the majority of the *T. cruzi* infections go undiagnosed
41 because of general mild symptoms and lack of access to medical care (11). Due to this fact, CD is
42 considered as a Neglected Tropical Disease whose improvement in diagnosis and treatment today
43 requires research and development efforts with non-profit interests. The highest prevalence of
44 Chagas disease has been reported in Bolivia (6.75–15.4 %), followed by Paraguay (0.69–9.3 %),
45 Panama (0.01–9.02 %), Brazil (0.8–1.30 %), Mexico (0.5–6.8 %) and Argentina (4.13–8.2 %)
46 (12). Citing a case, this disease causes almost 6% of the annual deaths in Mexico and the
47 seroprevalence can roughly be estimated at least in 3% due to a lack of active epidemiological
48 surveillance (most cases are detected during blood screening procedures in blood banks). Yet, less
49 than 0.5% of the infected individuals have access to treatment in this country as a result of
50 anachronisms in the normativity, among other failures in the public health system (13).

51 Even if CD mainly affects tropical countries, with nowadays ease of traveling and migration, other
52 countries are also being affected by this infection (14). Several cases have been reported in USA,
53 Canada, Europe and in Western Pacific regions like Japan and Australia (14–16). Notably, CD
54 continues to be an inconspicuous public health problem, with limited medical awareness, either
55 because it is commonly targeted in people with relatively low medical access or because it can
56 currently occur in unexpected regions. Thus, the treatment of CD urgently needs to generalize and
57 standardize diagnostic procedures.

58 Biosensors are relatively new analytical devices that can help to detect the presence of specific
59 compounds and pathogens in liquid environments and complex mixtures like: water and blood

60 serum. Although these devices have been formerly used in the alimentary industry (mostly to
61 detect toxins and infectious pathogens), they are been increasingly used to diagnose human
62 diseases (17). Therefore, these devices can be employed for the diagnosis of CD. The development
63 of biosensors requires a biological active component to be immobilized onto the surface of a
64 transducer. The selective recognition layer, towards *T. cruzi* specific antigens present in patients'
65 blood serum, can selectively detect the target analyte generating a signal response in the sensor
66 (see Figure 1). Depending on their transducing principle biosensors can be electrochemical,
67 acoustic or optic.

68 In this work, we firstly introduce a brief description of the disease. Secondly, we present a review
69 of biosensor technologies whose applicability to diagnose CD has been investigated. Finally, we
70 mention the benefits and drawbacks of applying biosensors as solutions to this major public health
71 issue and the infrastructure required to conduct biosensor experiments for this application.

72 2. Brief description of CD and current needs

73 CD passes through two successive stages: an acute phase and a chronic phase. The acute phase
74 occurs at the following 6-8 weeks after infection. The acute phase is followed by the chronic phase
75 of CD, which lasts for the rest of the life of the infected individual, and has different forms. In the

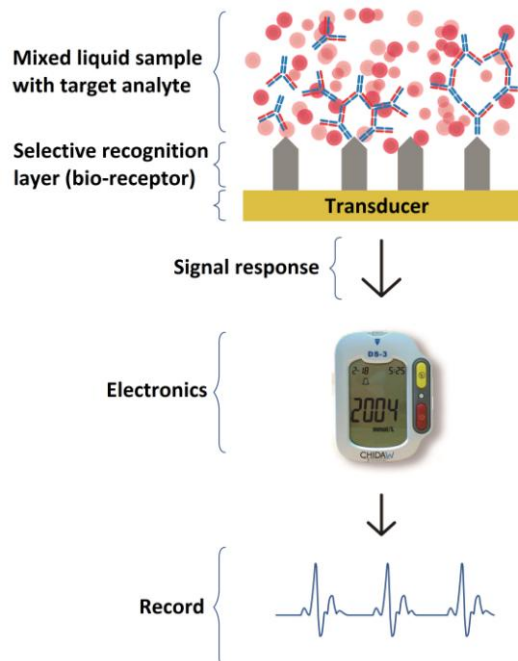


Figure 1. General scheme of a biosensor detection strategy. A biosensor is composed of a biochemical interface where specific bio-species are absorbed; a transducer which translates the recognition event to another physical response that can be measured and an electronic system which acquires and records the signal.

76 indeterminate form, an equilibrium between the parasite and the immunological response of the
1 77 infected individual is reached and most infected patients appear healthy, with no evidence of organ
2 78 damage that could be found by current standard methods of clinical diagnosis (8). About 50–70%
3 79 of infected individuals will remain in this condition for the rest of their lives. However, several years
4 80 after the chronic phase has started, 10–40% of infected individuals will pass to the cardiac form of
5 81 the disease and will develop injuries of various organs, mainly the heart, the digestive system, and
6 82 occasionally, the peripheral nervous system (8, 18). These important symptomatic changes occur
7 83 10–20 years after the acute phase of the disease and include a broad range of types of damage.
8 84 The clinical manifestations vary from mild symptoms to heart failure and, frequently, sudden
9 85 cardiac death (18). The acute phase of CD is recognized only in an estimated 1–2% of all
10 86 individuals acquiring the infection (8) due to a lack of access to sufficient medical care. Thus, more
11 87 than any other parasitic disease, CD is closely related to social and economic development.
12 88 Paradoxically, acute phase is the most appropriate period for drug treatment, showing relatively
13 89 high levels of sero-conversion, while organ damage is prevented (19). Conversely, it has been
14 90 shown that drug treatment with Trypanocidal therapy in patients with established Chagas
15 91 cardiomyopathy, can cause seroconversion, but does not stop cardiac clinical deterioration (20).

31 92 Given that no vaccine is currently available to prevent CD, vector control, diagnosis tests,
32 93 opportune drug treatment, and clinical follow-up are the most effective methods to fight against
33 94 the disease (21). Nevertheless, all these measures suffer of several hindrances imposed by the
34 95 synergistic negative effects of diverse vulnerability components of CD risk, such as ecological
35 96 factors (i.e. land-use changes) -that are broadening the contact zones between humans and
36 97 parasites (Lopez-Cancino et al., 2015)-, the chronic failure of health care policies hindering the
37 98 reduction of CD incidence (5), the limited awareness of physicians (22), and several socio-cultural
38 99 practices that perpetuate CD exposure in endemic regions (23). Health policies to control/reduce
39 100 vectorial exposure to CD in Latin America are challenged for the relatively high diversity of vectors
40 101 that shows a broad environmental tolerance. Likewise, a wide territory of America is suitable for CD
41 102 vectorial transmission (24–27).

53 103 In order to face the epidemiological challenges due to the increasing complexity of interactions
54 104 among the transmission routes of *T. cruzi* in endemic and non-endemic countries, access to early
55 105 diagnostic and treatment seems as the most cost-efficient ways to reduce the CD burden (11).
56 106 Several paths of scientific advances and discoveries envisage an optimistic future to reduce CD

107 burden coming from a better understanding of CD transmission and management toward its
108 interruption (28). The fact that the World Health Organization (WHO) has made a commitment with
109 Bill and Melinda Gates Foundation and other stakeholders to control the most neglected diseases by
110 2020, including CD among them, opens an opportunity window to orientate research priorities. This
111 commitment, launched in 2012, was called the London Declaration
112 (<http://www.unitingtocombatntds.org/>). However, claims have been raised to urge implicated
113 organizations to set the needed measures to reach these goals, among which improved diagnosis
114 (i.e. precision and accessibility) seems as one of the most important first steps (5).

115 Blood banks in endemic countries require fast and secure screening method for small and medium
116 health facilities, since screening for CD is mandatory in some endemic countries (8). Several
117 countries do not have an active program for CD detection and depend only for the blood bank
118 reports. The most important reason of this fact is the low feasibility to detect Chagas in patients.
119 Since, CD do not produce particular symptoms, there are not incentives from society. Nevertheless,
120 the bug bite is quite notorious and people can suspect that they are infected with *T. cruzi* when a
121 *chinchoma*¹ appears. In such cases, people can search medical assistance and be subjects of a
122 blood test.

123 Climate change and global warming increase the risk of rising CD burden in some regions. Climate
124 change impacts on vector-borne diseases (29) and is undoubtedly detonating variables that make
125 the CD transmission become potentially dangerous, as the WHO points out (30). Nevertheless, the
126 incidence of CD can be greatly reduced by residual insecticide-based vector control programs that
127 decrease the populations of the transmitting vectors and by improving housing (31).

3. Current detection technologies and their limitations

129 Currently, laboratory methods are employed to diagnose CD. Depending on the patients' phase of
130 infection some are more convenient than others. During the acute phase of CD, a large number of
131 parasites are present in the peripheral blood and can be diagnosed by direct microscopical
132 observation of fresh blood (parasitological test). However, for the chronic phase of CD the
133 diagnosis is not possible, due to the scarce parasitemia. Therefore, the immunodiagnosis is widely
134 used since nearly all *T. cruzi*-infected individuals in the chronic phase develop antibodies against
135 the complex antigenic mixture of the parasite (8).

¹ Name of the inflammatory injury after a bug bite.

136 Several immunodiagnosis tests are available, but mainly three conventional tests are widely used:
137 indirect haemagglutination (IHA), indirect immunofluorescence (IIF) and Enzyme Linked Immuno
138 Assay (ELISA). These tests present several limitations such as: (i) cross-reactivity with other
139 parasites; (ii) not 100% of sensitivity; (iii) the need to be performed in a laboratory; and (iv) a
140 long time is required to obtain the results. IHA test results can be obtained in about two hours,
141 whereas IIF results can be obtained after numerous steps in two hours and ELISA takes several
142 hours to carry out, including prior sensitization of microplates with *T. cruzi* antigens for about 12
143 hours (6). All these tests have to be performed in centralized laboratories; some of them require
144 sophisticated equipment and skilled technicians. Since none of these tests have a sensitivity of
145 100%, the WHO recommends conducting at least two conventional tests for a definitive diagnosis
146 of *T. cruzi* infection (8).

147 More recently, non-conventional tests, like rapid lateral flow (RLF) tests, are commercially available
148 in the market to detect *T. cruzi* infection using whole blood, serum or plasma (Sánchez-Camargo et
149 al. 2014). These tests are based in different tests principles: immunochromatography, particle
150 agglutination, immunofiltration or immunodot. They provide fast results (between 5 to 60 min
151 reading times) without the need of electrical equipment and they require low volume samples (5 to
152 150 µl). However, the sensitivities and specificities of such tests are lower than that of conventional
153 tests and they only provide qualitative or semi-quantitative results, which prevents obtaining
154 important test information like genetic lineage of the *T. cruzi* (32) and the immunoreaction
155 kinetics.

156 From a prospective point of view, it is important to discuss about another kind of technology, which
157 could be deployed for Chagas Disease diagnosis in the near future. Over the last decade, Shear-
158 Horizontal (SH) Surface Acoustic Wave (SAW) immunosensors (Love-SAW with a guiding layer)
159 have been developed for the diagnosis of various diseases (33). Such immunosensors exhibit a
160 high sensitivity and a very low limit of detection (in the order of pg/µl of blood serum). This
161 technology give very relevant results for the detection of antibodies, specific to certain diseases
162 (34). The only drawback of this technology is that a residual frequency or phase shift always
163 remains, which is induced by non-specific mass effects, i.e. a shift which does not correspond to
164 specific antigen-antibody interactions on the sensor surface (34). In order to drastically reduce or
165 avoid cross-reactions with other type of interactions that may lead to false positives, Rayleigh-SAW
166 generation, on the same piezoelectric substrate, seems to be very promising (35). In addition,

167 these waves can be used to generate fast fluid actuation to improve mixing and desorption
168 promoting faster molecular interactions. Indeed, Rayleigh-SAW liquid effects can induce intense
169 recirculation, actuation, heating or atomization, depending on the mechanical power conveyed by
170 these acoustic waves (36, 37). This recirculation can allow to re-suspend all non-specific species
171 that could settle and lead to non-specific responses.

172 **4. Biosensing research efforts for Chagas diagnosis**

173 Biosensors that have been investigated for the diagnosis of CD can be classified into
174 electrochemical -where amperometric (38–41) and impedimetric (42) sensors can be found- and
175 optical -where mainly Surface Plasmon Resonance (SPR) transducers (6) are found. Biosensors
176 could provide the benefits presented in Table 1 in comparison with other currently employed
177 techniques for the diagnosis of CD.

178 Pumpin-Ferreira et al., in 2005, reported a biosensor for the diagnosis of CD (38). It consisted on
179 an amperometric immunosensor. This biosensor required an electrochemical interaction and,
180 therefore, a potentiostat-galvanostat was required to conduct the measurements. Potentiostats are
181 powerful equipment, but they are large and heavy for a final portable biosensing system. Hence,
182 other electronics for biosensors characterization should be developed which provide higher
183 miniaturization and integration capabilities for portable systems.

184 Recently, Luz et al. (2015) presented the first biosensor for the diagnosis of CD based on SPR
185 transducers (6). They obtained the parameter related to the presence of antibodies anti-*T. Cruzi*
186 found in human serum in approximately 20 min. SPR transducing principle requires an optical
187 source for the laser generation and the integration of this source to the equipment, currently, leads
188 to high volume and heavy apparatus, only suitable for laboratory tests. Moreover, even if optical
189 biosensors can be very sensitive, the cost of SPR equipment is higher than USD \$50,000 and for
190 this reason, not many researchers can afford such systems (43).

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Table 1. Some methods for the diagnosis of CD.

Methods	Drawbacks	Benefits	References
Selective Media	<ul style="list-style-type: none"> - Microorganism needs to overgrowth fast - Long time to yield results - Needs a laboratory - Needs an aseptic work area - Needs trained personnel - Tedious procedure 	<ul style="list-style-type: none"> + Cheap + Easy to perform 	(44, 45)
ELISA	<ul style="list-style-type: none"> - Requires highly qualified personnel - Consumes a lot of time - Needs a laboratory - Expensive 	<ul style="list-style-type: none"> + High selectivity and sensitivity + Improves the time required to yield results + It works well for samples without interfering molecules 	(44-49)
Quantitative PCR	<ul style="list-style-type: none"> - Expensive - Needs trained personnel - Needs a laboratory - Difficult to perform 	<ul style="list-style-type: none"> + High selectivity and sensitivity + Improving the time required to yield results 	(45) (47-49)
Rapid test	<ul style="list-style-type: none"> - Specificity 96.8%. - Just qualitative results. - The method needs a tube, a measured volume of sample and reagent - Can present false positive 	<ul style="list-style-type: none"> + 15-25 min + High sensitivity of 99.5 % + Low cost (less than \$2 to the end user) 	(7, 50)

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Biosensors	- Not commercially available	+ No need of an aseptic working area	(6)
	- Large dimensions (currently)	+ Fast (real-time)	(38-42)
	- Needs a laboratory	+ Easy to perform. Not need of trained personnel	(17)
	- Further research and development is required for portable systems	+ <i>In situ</i> simple preparation	
	- High research cost	+ High analytical specificity	
		+ Reduction of reagents consumption	
		+ Reduced analysis time	
		+ High reliability	
		+ High sensitivity	
		+ Integration of multiple processes in a single device	
	+ Possible automation		
	+ Low cost of fabrication		

198 **5. Biosensors and their contribution to reduce CD burden**

199 An ideal serological test should be easy to perform in a single step, fast, cheap, require no special
200 equipment or refrigeration reagents and should have a sensitivity and specificity of 100%. Such a
201 test does not exist currently for the diagnosis of CD. Hence, new technologies, which combine,
202 robustness, simplicity, portability and rapidity with an effective sensitivity and selectivity could
203 contribute to more efficiently diagnose CD. There are evidences that show that biosensors could
204 meet most of these attributes for this application (6, 38). Biosensors could improve the diagnosis
205 and the patients' treatment follow-up, in terms of rapidity, real-time and low cost detection
206 compared to current detection technologies like Polymerase Chain Reaction (PCR) and ELISA. In
207 addition, the use of biosensors offers significant advantages like: small fluid volume manipulation,
208 a high integration capability that facilitates the development of portable devices and ease of use.
209 This should allow their use by non-specialized personnel in non-centralized laboratories (17).
210 Nevertheless, further research efforts are needed to achieve a biosensing portable device for CD
211 diagnosis.

212 The expected features of biosensors are high selectivity and sensitivity, real-time label-free
213 monitoring, easy to use, reliability, high miniaturization capabilities and low cost. Biosensors based
214 on optical and acoustic wave sensing technologies could meet these requirements in a near future
215 and seem to be very promising tools for this application. Such devices will lead to more sensitive
216 tests at lower reagent concentrations, allowing biosensing system users to: i) reduce the cost of
217 reagents; ii) obtain valuable quantitative information; and iii) extend the measurement range of
218 the assays.

219 **6. Infrastructure requirements**

220 To develop a portable biosensor system for the rapid diagnosis of CD, first of all, it is necessary to
221 integrate a transducer with a suitable sensitive bio-chemical layer. Some authors have already
222 achieved this milestone, as stated in Section 4. Additionally, the system requires the integration of:
223 i) an electronic read-out system, for the interrogation and signal acquisition; ii) a microfluidic
224 system, to handle bio-fluids; and iii) a thermal control unit, to keep the temperature stable during
225 the sample analysis. This last point could be avoided if it is proven that the temperature sensitivity
226 of the sensor in use is negligible for the experiments we are conducting or if a differential
227 measurement setup for a temperature compensation is employed (51). Furthermore, it is

228 important to mention, that a fully-automated feature is desirable for the complete system, in order
229 to run the sample analysis as comfortably as possible.

230 Nowadays, some companies offer commercial solutions for integrated biosensing systems that
231 could be employed to diagnose CD. However, most of this systems are still of considerable size,
232 weight and price, which prevents their wide use for field applications in low income communities.
233 Table 2 shows some integrated biosensing platforms currently available in the market and some of
234 their features. As can be appreciated in the table, all these systems require to be operated in a
235 laboratory due to their dimensions. If researchers choose a non-commercial solution, they require
236 to design and develop a system according to their needs. Nevertheless, this might allow them to
237 pursue a more compact, cost-effective and portable system.

238 *Table 2. Different biosensing systems currently available in the market.*

Product	Company Name	Transducer Technology	Dimensions (cm)	Weight (kg)
Q-Sense Omega Auto®	Q-sense	Acoustic	70×67×57	83
Biacore X100®	General Electric	SPR	59.6×56.3×59.3	47
AWS A20-F20®	AWsensors	Acoustic	77×75×45	60
OpenPlex®	Horiba	SPRi	49×30.4×48	15.6

239 **7. Conclusions**

240 Since there is not vaccine for CD, currently, the vector control and diagnosis tests are the most
241 effective methods for preventing the disease and apply effective drug treatments. Even if a
242 prophylactic or therapeutic vaccine could be achievable in next years, this would need to be part of
243 integrated efforts that include better diagnostic means, since a vaccine is unlikely to be enough to
244 stop the parasite transmission. Therefore, highly predictive diagnostic tests are required, not only
245 to estimate the real size of CD problem, but also to assess the effectiveness of every action
246 conducted towards a disease burden reduction.

247 Currently, there are three conventional tests to diagnose Chagas in its chronic phase: IHA, IIF and
248 ELISA. All of these tests have sensitivities under 100%. Therefore, the WHO recommends
249 performing at least two of these tests for a conclusive diagnosis, leading to a bottleneck of parasite
250 detection, caused by limited local availability of laboratories in which such tests can be performed.

251 In addition, the diagnosis of the disease is generally delayed due to logistic restrictions of potential
1 patients to access diagnostic centers.
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4 253 Non-conventional qualitative tests, like RLF tests, are currently commercially available. Some of
5 such tests can lead results within minutes, but cannot be considered as conclusive tests by
6 254 themselves. Biosensors could be employed to support RLF test results in the future, diminishing the
7 overall time to achieve definitive quantitative results. Moreover, biosensors could exceptionally
8 255 contribute to a fast and secure screening method for blood banks in small and medium health
9 facilities. Hence, biosensors could improve CD diagnosis and the patients' treatment follow-up, in
10 256 terms of rapidity, small sample volume, high integration, ease of use, real-time and low cost
11 detection compared to current conventional tests. Pursuing these goals is of considerable
12 257 importance and interest to diminish CD burden and to reduce the risk of disease spreading
13 intensified due to the climate change. Nevertheless, further research efforts are still needed to
14 258 develop portable biosensing systems in order to effectively employ this technology for CD
15 diagnosis.
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