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REVIEW ARTICLE

Congestive Heart Failure and Thyroid Dysfunction: The Role of the Low T_3 Syndrome and Therapeutic Aspects

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Abstract: ***Background:*** Both the morbidity and mortality rates from congestive heart failure (CHF) remain elevated despite the medical and non-medical management of the disease, thus suggesting the existence of residual risk factors such as thyroid dysfunction. Particularly, the 15-30% of patients with CHF, especially those with severe ventricular dysfunction, display the so-called *low T_3 syndrome* (LT3S), which seems to negatively affect the cardiovascular prognosis.

Objective: Only a few clinical trials have been carried out to verify both the safety and the efficacy of thyroid replacement in the LT3S, aiming to ameliorate the prognosis of CHF, and most of the results were controversial.

Methods: Since the aim of the present review was to briefly overview on both the indication and contraindication of triiodothyronine replacement in CHF and LT3S, the authors searched PubMed using the medical subject headings (MeSH) related to the following terms: "congestive heart failure" and "low T_3 syndrome" or "euthyroid sick syndrome" or "non-thyroidal sick syndrome". The research study only focused on the narrative and systematic reviews, randomized clinical trials and meta-analysis studies which were conducted before June 2019.

Results: Studies conducted in both animal models and humans provided controversial information about the effectiveness and safety of the T_3 replacement for improving ventricular dysfunction, particularly in the long-term.

Conclusion: Further clinical trials are needed to better explore the role of LT3S in patients with CHF and its consequent therapeutic strategy in this clinical setting.

Keywords: Hypothyroidism, low T_3 syndrome, euthyroid sick syndrome, non-thyroidal sick syndrome, congestive heart failure, levothyroxine, liothyronine, selenium.

1. BACKGROUND

The global estimated prevalence of congestive heart failure (CHF) is over 38 million affected individuals and represents a rising global epidemic with a relevant impact on public health [1]. It has been estimated that 5.7 million individuals live with CHF [2] in the United States, and similar findings were also described in Europe [3, 4]. The prevalence of CHF is increasing particularly in the elderly [5], more in men than in women [6]. A preserved or mildly reduced ejection fraction is more frequently observed than a seriously reduced one [7].

Despite the currently available therapies [8], both the morbidity and mortality rates remain elevated among patients with CHF [9] and clinical outcomes remain critical, thus suggesting the existence of other mechanisms that are involved in the pathophysiology of the CHF. Specifically, endocrine and metabolic dysfunctions should be considered as important contributors to the risk of either new onset or progression of CHF since largely described in the literature [10-14]. Patients with CHF and hormonal imbalance display worse outcomes related to myocardial insufficiency, and the adjustment of such alterations provides a relevant amelioration of the prognosis. Particularly, the so-called *low T_3 syndrome* (LT3S) represents a recurrent finding in CHF, and several evidences suggest that the less the level of circulating triiodothyronine (T_3), the worse the prognosis of the disease; thus, a thyroidal replacement can be useful to improve cardiovascular outcomes in this clinical setting.

Anyhow, proofs of safety and efficacy of the T_3 replacement in CHF are poor, particularly because of the exiguity of Randomized Controlled Trials (RCTs), and no guidelines are currently available to carefully suggest how to manage LT3S in these patients. Therefore, the aim of this review was to summarize the main cardiovascular effect of the thyroid hormone and to briefly overview both detrimental effects of T_3 deficiency and the efficacy/effectiveness of T_3 replacement in patients with CHF and the LT3S.

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2. METHODS

A literature search in PubMed was carried out using medical subject headings (MeSH) to search terms related to "congestive heart failure" and thyroidal dysfunction, including terms related to "low T_3 syndrome" or "euthyroid sick syndrome" or "non-thyroidal sick syndrome". The research focused only on narrative and systematic reviews, Randomized Clinical Trials, and meta-analysis conducted until June 2019.

3. THYROID HORMONE AND CARDIOVASCULAR SYSTEM

Since the first evidence supporting the beneficial effects of T_3 replacement in brain-dead organ donors and in cases of low cardiac output [15], further research has been conducted in order to clarify how the thyroid hormone influenced myocardial pump and cardiovascular function. After binding with its own intracellular receptor, T_3 rapidly increases the cardiac intracytoplasmic calcium release, and induces the transcription of the myosin heavy chain gene, enhancing the synthesis of thick filaments. Additionally, T_3 upregulates the transcription of genes encoding for both β-adrenergic receptors and sodium-potassium ATPase. Thyroid hormone also modulates non-genomic effects that principally involve membrane ion channels permeability, the actin-myosin polymerization and vascular smooth cells contraction. Globally, T_3 effects on cardiomyocytes lead to a relevant increase in myocardial contraction [16], heart rate, cardiac output and peripheral oxygen consumption and substrate requirements as well as a decrease in systemic vascular resistance. Consequently, low levels of thyroid hormone, as observed in clinical hypothyroidism, could induce bradycardia, decrease ventricular filling (diastolic dysfunction) and contractility, reduce cardiac load, impair left ventricular systolic function during exercise, and attenuate precordial sounds in case of pericardial effusion [17] (Fig. **1**). Additionally, T_3 seems to revert mitochondrial dysfunction after ischemia, preventing or limiting the detrimental effect of the ischemia-reperfusion syndrome.

The prevalence of thyroid hypofunction in CHF is not well established [18, 19] due to both the methods and cut-off points considered for the diagnosis, and a mutable prevalence of the amiodarone-induced thyroid dysfunction according to the different case studies examined. Thus, a great variability of overt hypothyroidism (OH) was found, ranging from 4% to 24% (most of them with subclinical hypothyroidism, SH) [20] with an elevated frequency of the so-called "low T_3 syndrome" (LT3S).

The prognosis of CHF and the risk of either the new onset or progression of the disease are strictly related to the grade of thyroidal impairment [21], as also observed by Ro, which found that hypothyroidism, considered as TSH >4.7 mUI/L, was associated with a 2-fold higher risk in hospitalization for CHF mainly in patients with previous cardiovascular diseases [22].

Also Chen [23] confirmed that TSH levels above the normal reference range were independently associated with an increased mortality and cardiovascular-related hospitalizations.

Triggiani and Iacoviello [21] reviewed the effect of thyroid dysfunction on myocardial insufficiency. Specifically, they found that OH increases the rate of mortality in patients with CHF, moreover an elevation in TSH values favourites left ventricle dysfunction leading to either a cardiac transplantation or medical devices implantation, and increasing the risk of hospitalizations for heart insufficiency.

Compared to the euthyroidism, in either healthy or patients with previous cardiovascular diseases, OH is associ-

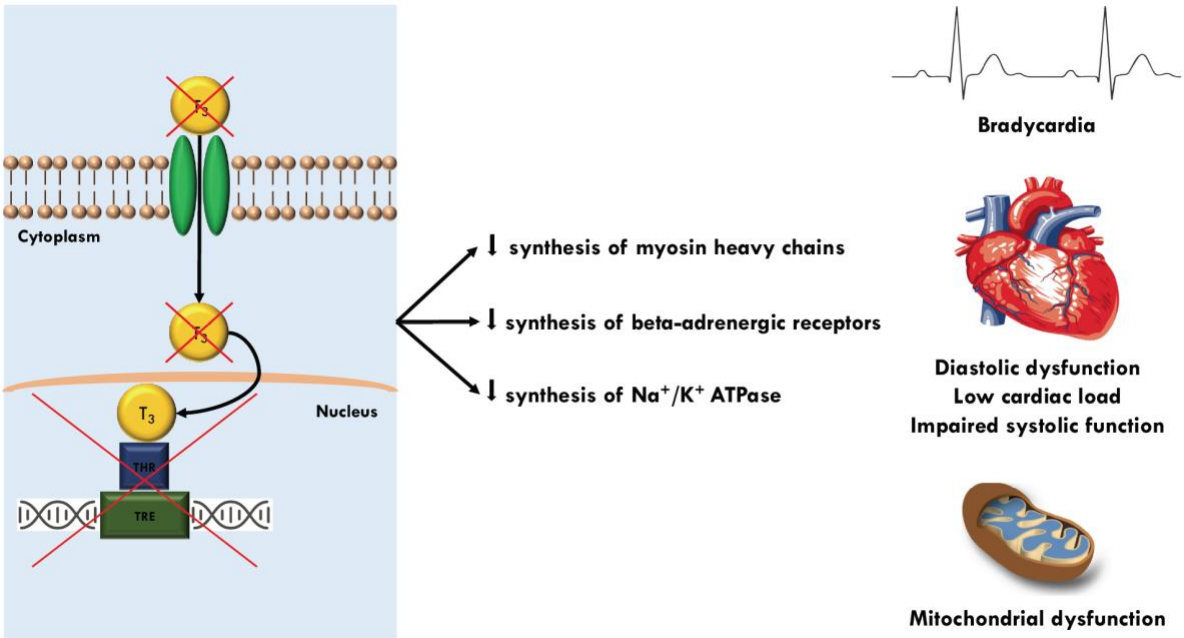

Fig. (1). Detrimental effects of the T_3 deficiency at the level of the myocardial tissue. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ated with a higher risk of cardiac mortality and all-cause mortality [24].

SH seems to generate similar but lighter cardiovascular effects compared to those described for OH [25]. The potential mechanisms responsible for diastolic dysfunction of the left ventricle in SH are associated with endothelial dysfunction and arterial stiffness, inflammatory state and cardiac remodelling [26]. SH is related to elevated morbidity, particularly for cardiovascular causes, and with a decreased myocardial contractility usually unmasked during the exercise [27]. Additionally, a higher rate of coronary occlusion after myocardial revascularization and an increased risk of CV mortality due to coronary ischemia and CHF were also found, particularly in patients <65 years [28, 29]. In the case of pre-existing heart failure, subclinical hypothyroidism with TSH ≥7 mIU/L and isolated low T_3 levels are associated with poor prognosis [19]. SH is independently associated with a greater likelihood of myocardial insufficiency onset and progression in outpatients with a previous CHF, leading to a high risk of death, heart transplantation or hospitalization for heart failure [30]. Thus, both morphological and functional alterations induced by OH and SH remain the main factors that explain an increased risk of onset and progression of CHF in these patients [31, 32].

The LT3S is frequently observed in patients with heart failure [33-35] as well in cachexia or malnutrition [36], ageing [37], critical illness, and is due to an increased level of cytokines such as Interleukine-6 and Tumor Necrosis Factor. However, both the frequency and severity of the LT3S are strictly related to the seriousness of CHF and this clinical matter becomes extremely relevant during the end-stage of the disease. The LT3S is largely ascribed to a drop in the rate of extrathyroidal conversion of T_4, attributable to a diminished activity of peripheral deiodinases. However, an increase in the T_4 catabolism due to an ectopic induction of the type 3 deiodinase activity in peripheral tissues and a central hypothyroidism, due to both a reduction in the thyrotropin releasing hormone release and a decrease in its peripheral effect, are also considered in the LT3S pathophysiology [38] (Fig. **2**).

Whether low levels of T_3 should be considered as an adaptive (beneficial) rather than a maladaptive condition remains doubtful, but a previous observation described the LT3S as an independent predictor of mortality in patients with CHF [39]. Additionally, the presence of the LT3S predicted worse hospital outcomes in patients with acute heart failure [40], and appeared to be an independent predictor for both all-causes and cardiac mortalities among critically ill patients with heart failure [41]. In one study, the 18% of patients with moderate-to-severe CHF presented the LT3S and this finding was an independent negative prognostic factor, but resulted reversible after heart transplantation [33] suggesting a mutual relationship between the two illnesses.

Selenium deficiency is frequently observed in patients with either heart failure or post-infarction syndrome and in those with the LT3S. An efficient function of numerous seleno-proteins, such as the glutathione peroxidase and iodothyronine deiodinases is allowed only in the case of normal levels of Selenium; thus, a deficiency in this ion leads to oxidative stress and endothelial dysfunction as observed in

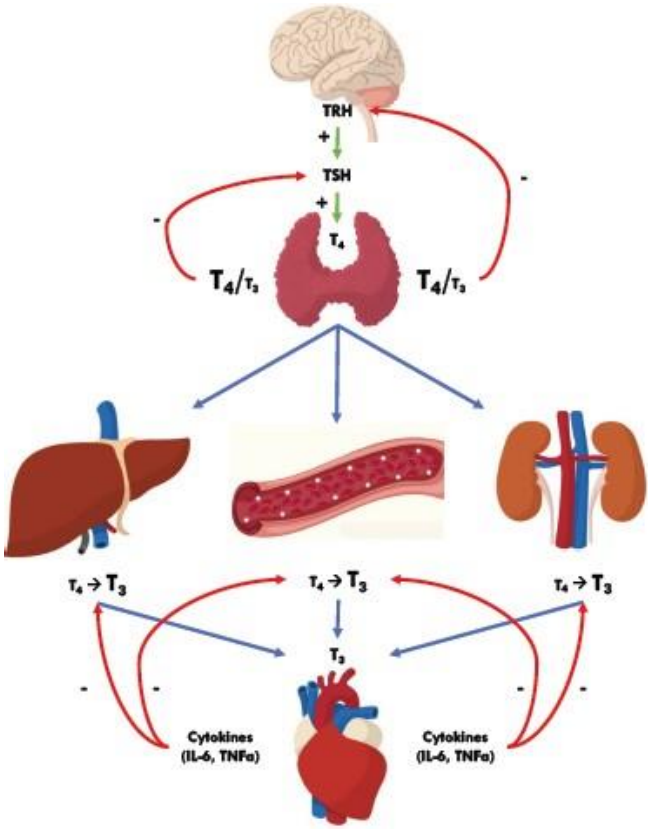

Fig. (2). Schematic representation of the regulation of thyroid hormone homeostasis. Thyroid hormone are largely secrete as T_4 rather than T_3 by the thyroid gland and the most part of the T_3 results from the peripheral conversion of T_4. The latter is catalysed by a class of seleno-proteins known as desiodases. Desiodase type 1 and 2 are mainly express at the level of the thyroid gland, liver, kidney, endothelial surface, and are responsible for the most relevant production of T_3 in the human body. Conversely, desiodase type 3 converts the T_4 in T_3 reverse which is an inactive form of thyroid hormone. High circulating levels of IL-6 and TNF-a, which are usually observed in myocardial infarction and heart failure, reduce the expression of both the type 1 and type 2 desiodases, and result in a significant reduction of the rate of the peripheral conversion of T_3 leading to the so called LT3S. The more the seriousness of the heart failure the great the severity of the LT3S that may contribute to additionally impair the ventricle dysfunction prompting a sort of vicious circle. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

patients with CHF [42], and can endorse the LT3S. Despite the fact that Sodium Selenite partially corrects the oxidative stress generated by high concentrations of interleukin-6, it does not prevent the interleukin 6-induced deiodinase dysfunction, and is not able to restore a normal concentration of T_3 in critically ill patients [43]. This hypothesis was also confirmed in a cohort of patients with CHF and reduced ejection fraction in which Selenium supplementation was not able to replace the normal levels of T_3, and consequently was not able to restore the left ventricle pump efficiency [44]. These findings, therefore, suggested the lack of correlation between serum Selenium concentration and serum T_3 concentration.

4. THYROID REPLACEMENT IN CHF

Despite the amelioration of the medical and non-medical management of CHF, both the morbidity and mortality rates remain elevated in this clinical setting suggesting the presence of residual risk factors. Specifically, thyroid dysfunction can contribute to increase the risk of morbidity and mortality in patients with CHF, as well as the LT3S. As previously described, T_3 directly produces positive chronotropic and inotropic effects at the level of the myocardium. Moreover, T_3 significantly increases tissue thermogenesis leading to a peripheral vasodilatation with a consequent decrease of arterial filling, which activates the renin-angiotensin-aldosterone system. The latter significantly increases the sodium reabsorption at the level of the kidney, and contributes to restoring both the cardiac output and pump efficiency [25].

T_3 also prompts protective effects at the level of mitochondria, as observed in one study in which the intramitochondrial concentration of the peroxisome proliferator-activated receptor gamma coactivator 1-alfa or PGC-1alfa, a key regulator of energy metabolism, and the synthesis of several micro-RNAs involved in the regulation of gene expression with cardioprotective effects (regulation of mitochondria membranes integrity, defensive systems against oxidative stress, etc) rapidly increase 6 hours after the exposition to T_3 [45]. In a rat model of post-myocardial infarction, a low dose of levothyroxine (1,5 ng/100g of body weight) administered for three consecutive days produced an increase in the left ventricle systolic pressure and a reduction in the left ventricle end-diastolic pressure. However, only after the administration of the 3,5-diiodothyropropionic acid (DITPA), a thyroid hormone analogue with high affinity for both thyroid receptors α and β, a persistent improvement of the left ventricle performance was finally observed. Therefore, these results suggested that thyroid hormones with high affinity and prolonged interaction with their own receptor could be considered in the treatment of CHF to improve the prognosis of the disease [46]. DITPA displayed beneficial effects on animal models of myocytes after ischemia, including the restoration of repolarizing transient outward potassium current that increases the calcium-mediated contraction [47] of myocytes. Furthermore, DITPA was able to regulate the gene expression involved in myocardial remodelling [38, 48, 49], and to increase the coronary microvasculature [50, 51] leading to a consequent reduction of the ischemic area after a coronary obstruction.

Hamilton *et al*. [52] evaluated haemodynamic effects after a short term intravenous administration of T_3 in 23 patients with advanced CHF, and demonstrated that T_3 administration was well tolerated without any significant change in heart rate or metabolic rate and induced a relevant increase in cardiac output due to an important reduction in systemic vascular resistance. In addition, a randomized double-blind comparison study in 19 patients with heart failure (DITPA versus placebo) [53] confirmed the potential beneficial effects of thyroid hormone analogues in the treatment of CHF. Nevertheless, long-term efficacy of DITPA intended to improve both the signs and symptoms of CHF led to equivocal results. Indeed, in a phase II study [54], the long term treatment with DITPA versus placebo highlighted a low efficacy and a poor safety profile due to the onset of relevant side effects, particularly at the level of bone, which conditioned a high dropout rate [55].

Short term treatment with synthetic T_3 induced similar findings compared to those previously described for DITPA. In one study, 20 patients with CHF due to a dilatative myocardiopathy (12 post-ischemic and 8 primitive) were randomized to a 3-day continuous intravenous infusion of T_3 versus placebo (saline 0.9%). Short-term T_3 replacement therapy significantly improved the neuroendocrine profile (reduction of plasmatic aldosterone and serum catecholamines) and the ventricular performance (rise in left ventricular systolic volume and reduction in left ventricle end-diastolic volume) [56]. Contrariwise, a long term treatment with oral T_3 produced equivocal results. According to one study [57], a persistent oral supplementation of liothyronine might not be beneficial in patients with stable CHF with only a modest degree of systolic dysfunction and low-normal serum T_3 concentrations. On the other hand, a T_3 supplementation with a once-daily dose of 25 mcg of synthetic liothyronine for 6 weeks in patients with CHF and stable moderate-to-severe left ventricle impairment (ejection fraction <40%) on top of the standard cares seemed to safely improve echocardiographic parameters over time [58]. Recently, in a phase II trial, Pingitore and Colleagues [59] studied the effect of a six-month T_3 replacement in 37 patients with a recent hospitalization for acute myocardial infarction and the LT3S. Exactly, they randomized 19 patients to a T_3 treatment (15 mcg/m^2/daily) versus 18 patients on placebo, and monitored both thyroid (serum concentration of TSH, fT3 and fT4) and left ventricle function (left ventricle volume, stroke volume, ejection fraction and wall motion score index by a cardiac Magnetic Resonance) at the time of discharge and 1 and 6 months later. The randomization started during the hospitalization, showing a significant increase of T3 levels as soon as at the time of the discharge and at 1 month without any complications (such as arrhythmias or other signs and symptoms of hyperthyroidism); despite a slight but significative reduction of the wall motion score index in both groups, the stroke volume increased during follow-up in the group on T_3 replacement, indicating that this treatment resulted safe and able to improve the left ventricle function in people with a recent myocardial infarction and the LT3S.

5. DISCUSSION

Worldwide, cardiovascular diseases represent one of the most relevant causes of morbidities and mortality and both the incidence and prevalence of the disease and its complications, such as CHF, are expected to rise consistently over the next decades. Thus, a growing number of patients with CHF could require composite treatments to avoid these complications. Despite solid evidences have previously demonstrated the efficacy of beta-blockers [60], angiotensin-converting enzyme inhibitors [61] and, more recently, of a neprilysin inhibitor [62] in reducing the risk of both all-causes and cardiovascular mortality in patients with reduced ejection fraction, CHF-related complications remain elevated.

Thyroid dysfunction represents a common finding in patients with CHF and in some cases the first is related to the presence of the latter, or it is the consequence of medical

treatment (i.e. Amiodarone). Particularly, the frequency and severity of the LT3S are usually related to the seriousness of the pump function impairment in CHF, and the two clinical conditions frequently coexist as the consequence of a chronic exposure to pro-inflammatory cytokines and increased oxidative stress. When the normal levels of T_3 are restored in CHF associated with the LT3S, the prognosis could improve according to several pathophysiological mechanisms [63]. In animal models, both thyroid hormone and a thyroid analogue (DITPA) have shown to reduce the post-ischemic pathological remodelling of the myocardium, and to improve the left ventricle function. In humans, the administration of T_3 seems to quickly improve the ventricle contraction specifically after a brief period of high dose intravenous administration (3 days), but the durability of this effect appeared limited over time, and restricted to patients with a serious impairment of ventricle function or in those with extremely low levels of serum T_3. Despite some positive long-term evidences supporting the efficacy of a chronic oral supplementation of T_3 in patients with a stable CHF with reduced ejection fraction and the LT3S, currently available data do not allow conclusive agreement about the management of the LT3S in this clinical setting. Additionally, long term exposure to a high dose of T_3 could produce relevant side effects over time, particularly at the level of the cardiovascular system and bones.

Selenium deficiency is frequently observed in CHF, and can play a relevant role in the pathogenesis of the LT3S. Adequate plasmatic levels of Selenium normally restore the activity of several seleno-proteins, contributing to renovate defensive mechanisms against oxidative stress and inflammation and to improve both peripheral thyroid hormone metabolism and cardiovascular outcomes. Only a few studies have addressed these issues, reporting unclear or controversial results; thus, the contribution of the Selenium replacement in patients with CHF and the LT3S appears minimal and further therapeutic strategies are needed to improve the prognosis of patients with serious ventricle systolic dysfunction, low levels of T_3 and Selenium deficiency.

CONCLUSION

In conclusion, the efficacy of a long-term thyroid replacement in CHF and the subset of patients who require the treatment remain questionable. Similarly, the strategies of thyroid replacement are uncertain. Intravenous T_3 administration is an uncomfortable and potentially dangerous way of administration that can be used to quickly improve the left ventricle function but only in hospitalized patients, admitted for acute or severe heart insufficiency, and for a brief period of time. Oral supplementation of T_3 could be considered as a chronic replacement in case of very low levels of T_3 and in patients with a severe ventricle dysfunction. Due to potential side effects, including arrhythmias, acute coronary disease, osteoporosis and a increased risk of bone fractures, T_3 replacement should be carefully recommended only in patients without severe comorbidities. Thyroid hormone analogues with high affinity for thyroid receptors displayed low cost-effectiveness when administered for improving hemodynamics in CHF; thus, it did not receive the approval for clinical usage in this clinical setting. Despite the Selenium deficiency being more prevalent in patients with CHF and the LT3S, its correction did not significantly improve both cardiovascular hemodynamic and peripheral thyroid metabolism. Additional studies [64] are needed to better understand the pathophysiology of thyroid dysfunction in CHF, the relationship between cardiovascular hemodynamic and hormone deficiency. Additionally, future RCTs and observational trials are required to produce a solid scientific evidence supporting either the efficacy or effectiveness of hormonal replacement therapies in patients with CHF with systolic impairment [65].

LIST OF ABBREVIATIONS

CHF	=	Congestive Heart Failure
DITPA	=	3,5-Diiodothyropropionic Acid
LT3S	=	Low T_3 Syndrome
LT4	=	Levothyroxine
OH	=	Overt Hypothyroidism
RCTs	=	Randomized Controlled Trials
SH	=	Subclinical Hypothyroidism
T_3	=	Triiodothyronine.

AUTHOR CONTRIBUTIONS

Giuseppe Lisco: project leader, manuscript writer; Anna De Tullio: manuscript writer; Massimo Iacoviello: manuscript reviewer; Vincenzo Triggiani: project leader, manuscript reviewer.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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