

Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Short review

Cardiac troponin elevation in patients with influenza virus infections

Giuseppe Lippi ^a, Fabian Sanchis-Gomar ^{b,*}^a Section of Clinical Biochemistry, University of Verona, Verona, Italy^b Department of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Valencia, Spain

ARTICLE INFO

Article history:

Received 3 February 2020

Accepted 2 June 2020

Available online 10 June 2020

Keywords:

Influenza

Cardiac troponin

Myocardial injury

Cardiac injury

ABSTRACT

The association between acute infections and cardiac injury, including myocarditis and acute myocardial infarction, is now well established. We have performed a systematic literature review for analyzing the results of epidemiological studies that measured cardiac troponins (cTn) in patients with Influenza virus infections. Overall, 14 articles were finally identified and analyzed. Taken together, the results of the scientific literature suggest that cTn elevation is a relatively rare phenomenon in patients with Influenza virus infection, with frequency generally comprised between 0 and 33%, more likely in elderly patients with significant comorbidities. In patients with modest cTn elevations, this phenomenon is apparently self-limited, transient and reversible, and especially involves patients with Influenza A (especially H1N1). In the minority of patients exhibiting an abrupt appearance of cardiovascular symptoms and concomitant elevation of cTn values, the relative increase of this biomarker reflects the presence of an underlying cardiac injury, that can be either myocarditis or an acute ischemic episode. Enhanced cTn values can also be more frequently observed in Influenza patients with complicated disease, in those developing acute respiratory distress syndrome and cardiac dysfunction, as well as in those at higher risk of death. cTn measurement shall be considered a valuable option in all patients developing acute cardiovascular symptoms during Influenza virus infections, as well as in those bearing cardiac or extra-cardiac comorbidities who bear a higher risk of complications.

The existence of a strong epidemiological, biological and clinical association between acute infections and acute coronary syndrome (ACS) is now well established [1]. As regards respiratory infections, the very first public report of excess mortality from cardiovascular disease during epidemics of Influenza virus infections has been described in the early

1930s by Selwyn D. Collins [2]. In this original report, Collins carried out a comprehensive analysis of mortality data between the years 1915 and 1929 and concluded that the excess mortality ranged between 40 and 90% during 11 previous Influenza virus epidemics. This seminal report paved the way to many further studies, which were all virtually concordant

* Corresponding author. Department of Physiology, Faculty of Medicine, University of Valencia, Av. Blasco Ibañez, 15, 46010, Valencia, Spain.

E-mail address: fabian.sanchis@uv.es (F. Sanchis-Gomar).

Peer review under responsibility of Chang Gung University.

<https://doi.org/10.1016/j.bj.2020.06.001>

2319-4170/© 2020 Chang Gung University. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

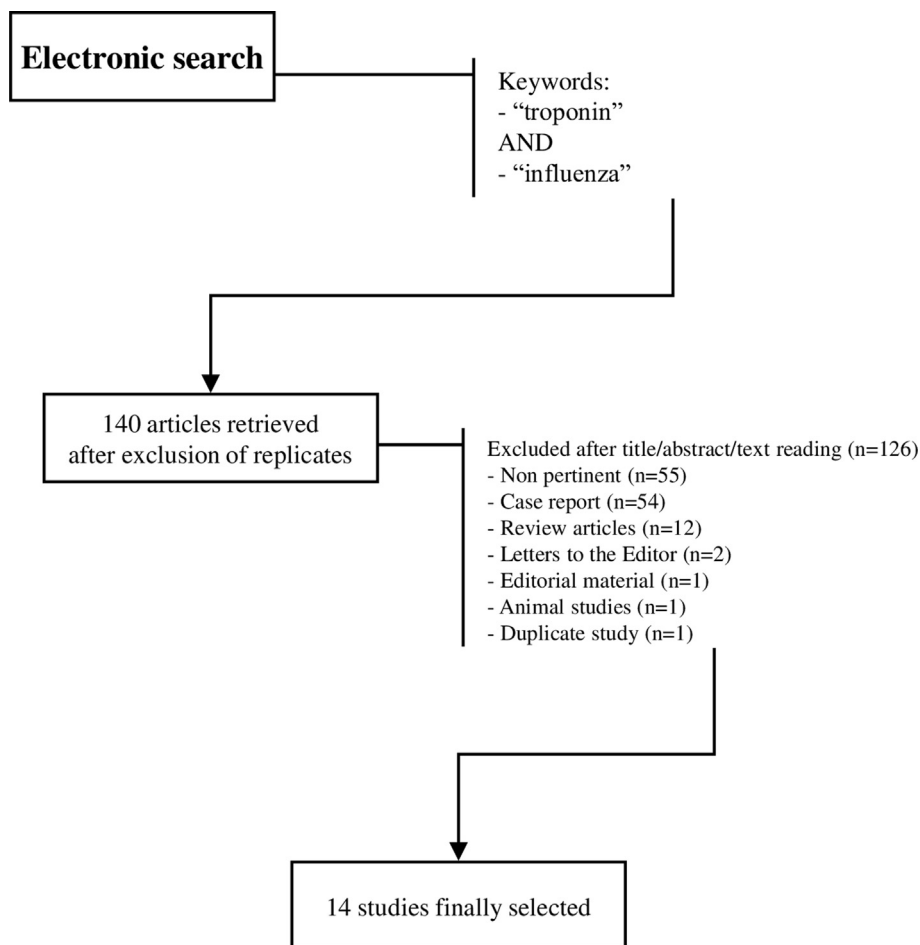


Fig. 1 Summary of search criteria and outcome.

to confirm that Influenza and other upper respiratory viral infections are accompanied by an excess cardiovascular morbidity and mortality [3].

In the meta-analysis published in 2015 by Barnes et al. [4], a recent diagnosis of Influenza virus infection was found to be associated with 2-fold (odds ratio (OR) 2.01; 95% confidence interval (95% CI), 1.47–2.76) higher risk of developing an episode of acute myocardial infarction (AMI). Even more importantly, vaccination against Influenza viruses was found to be associated with a 29% lower risk of AMI (OR, 0.71; 95% CI, 0.56–0.91). According to the data more recently published by Ruane et al. in 578 patients with angiographically confirmed AMI [5], symptoms of respiratory infection were rather commonplace in these patients, being reported in approximately 20% of cases within 35 days prior to the onset of the ischemic episode. This then translated into a 17-fold higher risk of developing an ACS (relative risk (RR), 17.0; 95% CI, 13.2–21.8) within 1–7 days after onset of respiratory infection symptoms, gradually decreasing over time and becoming as low as 1.7-fold (RR, 1.7; 95% CI, 1.0–2.9) 1 month after appearance of respiratory symptoms.

The important, virtually unquestionable, association between Influenza virus infections and cardiac diseases discloses foremost perspectives on the role of laboratory

diagnostics. The detection of cardiac injury, either ischemic, inflammatory, infective, toxic or even traumatic, is now strongly dependent on the demonstration of increased values of cardiac troponin (cTn) I or cardiac troponin (cTn) T, especially when the biomarkers are measured with the novel generation of high-sensitivity (HS) immunoassays [6,7]. Since it seems reasonable that cTn assessment may also have a clinical role in patients with Influenza virus infections, we carried out a systematic literature review for analyzing the results of epidemiological studies which measured cTn in patients with influenza and thus provide some indications on its potential clinical usefulness.

Literature search

An electronic search was conducted in the three most widely used scientific repositories Medline (with PubMed interface), Scopus and Web of Science [8], using the generic keywords “influenza” AND “troponin”, with the purpose of identifying all clinical studies which have measured the concentration of cTn in patients with Influenza virus infections. No date or language restrictions were applied. All references of the

Table 1 Summary of epidemiologic data reporting cardiac troponin values in patients with Influenza virus infection. Studies marked in bold used high-sensitivity assays.

Study	Study population	Cardiac troponin assay and relative cut-off	Diagnosis of influenza	Results
Greaves et al., 2003 [9]	152 patients with Influenza (mean age, 39 years; 49% women)	CS-cTnT (<10 ng/L) and CS-cTnI (<100 ng/L)	Hemagglutination inhibition assay	No patient displayed elevation of either cTn above the URL
Ison et al., 2005 [10]	30 patients with Influenza (mean age, 21 years; 70% women)	CS-cTnI (<50 ng/L)	Lateral-flow immunoassay	No patient displayed elevation of either cTn above the URL
Brown et al., 2011 [12]	48 patients with Influenza A H1N1 virus infection (mean age, 41 years; 70% women)	CS-cTnI (400 ng/L)	rRT-PCR	cTnI values 4-fold higher in patients with acute respiratory distress syndrome
Pečavar et al., 2011 [11]	196 patients with influenza-like illness, 66 of whom (33.7%) positive for Influenza A H1N1 (age range, 17–100 years; 49% women)	Unspecified	rRT-PCR	cTn values 11% higher in patients with Influenza A H1N1 infection
Chacko et al., 2012 [13]	37 patients with complications of Influenza A H1N1 virus infection (mean age, 39 ± 13 years; 68% women)	CS-cTnI (<1500 ng/L)	rRT-PCR	cTn values exceeding the diagnostic cut-off in 46% of patients and associated with 9-fold higher risk of death
Song et al., 2012 [14]	71 patients with Influenza A H1N1 virus infection (age range, 29–84 years; 56% women)	CS-cTnI (unspecified cut-off)	Unspecified	cTn values similar in patients with or without cardiovascular complications
Fagnoul et al. 2013 [15]	39 patients with Influenza A H1N1 virus infection (mean age, 48 ± 17 years; 52% women)	HS-cTnI (unspecified cut-off)	rRT-PCR	cTn values increase in parallel with the severity of cardiac dysfunction
Han et al., 2015 [16]	40 patients with Influenza A H7N9 infection (60 ± 15 years; 45 women)	Unspecified cTnI assay (<13 ng/L)	rRT-PCR	cTn values higher during infection and also higher in patients with more severe form of disease
Ludwig et al., 2015 [17]	600 patients with laboratory-confirmed influenza (no demographic data available)	Different facilities used different tests with varying reference ranges	Different facilities used different tests	cTn values exceeding the local cutoff in 24% of patients
Wang et al., 2017 [18]	24 patients with Influenza A H7N9 (mean age, 59 ± 18 years; 29% women) and 22 patients with Influenza A pH1N1 (mean age, 42 ± 16 years; 62% women) infections	Unspecified cTnI assay (unspecified cut-off)	rRT-PCR	cTn values increased in 33% H7N9 patients and in 5.0% H1N1 patients
Qian et al., 2017 [19]	15 patients with severe Influenza A H1N1 infection (47% women; mean age was 53 ± 13 and 61 ± 15 years in those who survived or died)	Unspecified	rRT-PCR	cTn values 3.5-fold higher in patients who died compared to those who survived
Ito et al. 2019 [20]	20 patients with Influenza virus infection (15 with type A and 5 with type B; mean age, 43 ± 13 years; 75% women)	HS-cTnT (<14 ng/L)	Immunochromatography	No patient displayed elevation of either cTnT above the URL
Harris et al., 2019 [21]	1131 patients with Influenza virus infection (mean age, 71 ± 12 years; 61% women)	Unspecified cTnI assay (<300 ng/L)	rRT-PCR	cTn values exceeding the diagnostic cut-off in 1.1–3.5% of patients
Pizzini et al. 2020 [22]	264 patients with laboratory-confirmed Influenza virus infection (mean age, 51 ± 22 years; 50% women)	HS-cTnT (<14 ng/L)	rRT-PCR	cTn values 9-fold higher in patients who died compared to those who survived

Abbreviations: cTnI: cardiac troponin I; cTnT: cardiac troponin T; CS: contemporary sensitive; HS: high-sensitivity; rRT-PCR: real-time reverse transcriptase polymerase chain reaction; URL: upper reference limit.

Studies in bold used high-sensitivity assays for troponin testing.

initially selected items were accurately scrutinized for detecting additional pertinent documents. All items identified according to these search criteria were systematically reviewed by the two authors (GL and FSG) and potential disagreement was resolved by discussion. Information on sample size, characteristics of the study populations as well as on the methods used for diagnosing Influenza and measuring cTn were reported, when available. This critical review of the literature was conducted in accordance with the Declaration of Helsinki and under the terms of relevant local legislation.

Evidence from clinical studies

Our electronic search in the three scientific repositories allowed the identification of a total number of 140 items after exclusion of duplicates. Overall, 126 documents (90.6%) ought to be excluded after abstract and/or full text reading (when available), because were (a) non-pertinent to the scope of this article or did not contain data on cTn values ($n = 55$; 43.7%), (b) single or multiple case reports ($n = 54$; 42.9%), (c) review articles ($n = 12$; 9.5%), (d) letters to the editor ($n = 2$; 1.6%), (e) editorial material ($n = 1$; 0.8%); (f) animal studies ($n = 1$; 0.8%), or (g) duplicate studies ($n = 1$; 0.8%) [Fig. 1]. Inter-rater reliability was excellent ($k = 0.997$; $p < 0.001$). Overall, 14 articles were finally selected for being discussed in this critical literature review [Fig. 1; Table 1].

The very first study which assessed cTn values in patients with acute influenza infection was published by Greaves et al. [9] in 2003. The study population consisted of 152 patients, recruited from primary care and University health centers, in whom both cTnI and cTnT were measured on days 1, 6 and 21 after receiving a diagnosis of Influenza virus infection (95% infected by Influenza A-H3N2 virus, 1% by Influenza A-H1N1 virus and 4% by Influenza B virus, respectively). Throughout the study period (i.e., between days 1 and 21 after the initial diagnosis of Influenza virus infection), no patients showed TnI or TnT elevations above the upper reference limit (URL).

Two years later, in 2005, Ison et al. [10] carried out an observational cohort study, in which cTnI was measured in 30 patients on days 1, 4, 11 and 28 after receiving a diagnosis of Influenza virus infection. Even in this study, no patient displayed elevations in cTnI above the method-specific URL.

Another study has then been published by Pecavar et al. [11] who studied 196 patients with influenza-like illness, 66 of whom (33.7%) testing positive for Influenza A H1N1 virus. The concentration of cTn (no information is available on the type of the immunoassay, nor on the diagnostic cut-off) was found to be significantly higher in patients with Influenza A H1N1 virus infection than in those without (i.e., 162 ± 63 vs. 146 ± 58 ng/L; $p < 0.01$).

Brown et al. [12] then measured cTnI in 48 patients admitted to the intensive care unit (ICU) for worsening of Influenza A H1N1 virus infection. The mean cTnI concentration was 30 ng/L (95% CI, 10–200 ng/L) in the entire cohort, but the value was nearly 4-fold higher (80 ng/L; 95% CI, 20–260 ng/L) in those who developed acute respiratory distress syndrome (ARDS) during ICU stay. Overall, cTnI value was found to be higher than the diagnostic cutoff in 9% of patients.

Chacko et al. [13] also studied 37 patients who were admitted to the ICU for urgent management of severe complications of Influenza A H1N1 virus infection. The baseline cTnI value at ICU admission was 3100 ± 7700 ng/L, further increasing to $10,800 \pm 22,600$ ng/L during ICU stay. Values exceeding the locally defined diagnostic cut-off (i.e., 1500 ng/L) were recorded in 17/37 patients (46%) and were also associated with a nearly 9-fold higher risk of mortality (OR, 8.7; 95% CI, 1.5–60.0).

Song et al. [14] retrospectively reviewed the clinical records of 71 patients included in the 2009 Influenza A H1N1 registry database, to explore potential associations between cTn and cardiovascular complications. Overall, cardiovascular complications could be identified in 6/71 patients (8.4%), but the values of cTnI (20 ng/L; interquartile range (IQR), 10–80 ng/L) were virtually identical to those of patients without cardiovascular complications (20 ng/L; IQR, 10–40 ng/L; $p = 0.640$).

Fagnoul et al. [15] conducted a retrospective analysis of 39 patients admitted to the ICU for complications of Influenza A H1N1 virus infection. After patients were classified according to echocardiographically assessed cardiac dysfunction, a gradual increase of cTn values could be observed from those without myocardial dysfunction ($n = 11$; 20 ng/L; IQR, 10–150 ng/L), to those with predominant left ventricular dysfunction ($n = 17$; 30 ng/L; IQR, 10–250 ng/L), up to those with predominant right ventricular dysfunction ($n = 11$; 40 ng/L; 95% CI, 10–440 ng/L).

Han et al. [16] retrospectively reviewed the clinical records of 40 patients with laboratory-confirmed Influenza A H7N9 infection. In all these patients the value of cTnI had been measured during and after Influenza A H7N9 virus infection. After patients were classified according to their Acute Physiology and Chronic Health Evaluation II (APACHE II) score, cTnI consistently increased from those with the lowest score (7 ng/L; range 0–32 ng/L) to those with the highest score (1145 ng/L; range 73–3024 ng/L; $p < 0.05$). Interestingly, cTnI values were also considerably higher during acute influenza illness than after recovery in patients with both APACHE II scores III (388 ng/L and range 3–1149 ng/L vs. 26 ng/L and range 0–91 ng/L; $p < 0.05$) and IV (1145 ng/L and range 73–3024 ng/L vs. 35 ng/L and range 83–616 ng/L; $p < 0.05$). Similarly, the percentage of patients with elevated cTnI values was considerably higher during acute influenza illness (~75% and 100% in APACHE II groups III and IV) than after recovery (~50% and ~30% in APACHE II groups III and IV).

In a very large U.S. veterans study, Ludwig et al. [17] reviewed the clinical records of 600 patients with laboratory-confirmed Influenza virus infection, 143 of whom (24%) displayed a cTn value exceeding the URL (different facilities used different tests with varying reference ranges).

Wang et al. [18] studied 46 critically ill patients who ought to be admitted to the ICU for complications of Influenza A H7N9 virus ($n = 24$; mean age, 59 ± 18 years; 29% women) or Influenza A pH1N1 virus ($n = 22$; mean age, 42 ± 16 years; 62% women) infections. In 8 patients the value of cTnI was found to be increased over the URL (19.5%; 7 with H7N9 and 1 with H1N1, i.e., 33.3% vs. 5.0%; $p = 0.022$) out of the 41 cases in whom the biomarker could be measured. Interestingly, the interval between onset of cTnI elevation and development of

adverse cardiac events was 9.5 and 7.0 days in patients with H7N9 and H1N1 viral infections, respectively.

Qian et al. [19] also studied 15 patients with severe Influenza A H1N1 virus infection. The cTn values were found to be substantially higher in patients who died than in those who survived (520 vs. 150 ng/L; $p = 0.018$).

Ito et al. [20] studied 20 adult patients diagnosed with Influenza virus infection. The value of cTnT measured with a HS immunoassay 2 and 4 weeks after the diagnosis of Influenza infection was found to be lower than the URL in all patients.

Harris et al. [21] recently published the results of a retrospective observational study including all adult patients diagnosed with Influenza virus between August 2017 and March 2018. Overall, cTnI elevations (i.e., >300 ng/L) were found in 30/863 (i.e., 3.5%) patients diagnosed with Influenza A virus infection and in 3/270 (i.e., 1.1%) of those diagnosed with Influenza B virus infection, respectively ($p = 0.054$).

Interesting evidence has been recently reported by Pizzini et al. [22], who carried out a retrospective study for establishing the potential prognostic significance of cTnT in patients diagnosed with Influenza virus infection. The authors measured cTnT with a HS immunoassay in 264 patients with laboratory-confirmed influenza virus infection (184 with Influenza A virus and 80 with Influenza B virus infections, respectively). Overall, cTnT was found to be higher in patients with Influenza A virus than in those with Influenza B virus infection (27 ± 67 vs. 16 ± 36 ng/L; $p = 0.04$). When the entire cohort of patients was stratified according to cTnT value (i.e., below or above the URL of 14 ng/L), patients with cTnT >14 ng/L underwent higher rates of inpatient treatment (87% vs. 37%; $p < 0.001$) and had a borderline statistically significant higher risk of 30-day mortality (7.2% vs. 2.3%; OR, 3.38; 95% CI, 0.93–12.33; $p = 0.065$). After dividing patients into tertiles of cTnT, those in the highest tertile had a nearly 9-fold higher risk of death at 30 days than those in the lowest tertile (OR; 8.96; 95% CI, 1.06–75.85; $p = 0.02$). A cTnT value > 46.4 ng/L displayed the best diagnostic performance for predicting 30-day acute cardiovascular events (0.70 sensitivity and 0.80 specificity, respectively).

Discussion

A vast array of myocardial injuries may develop in patients with infectious diseases, including those suffering from Influenza virus infection, the most frequent of which are myocardial ischemia and myocarditis [23]. This straightforward evidence further emphasizes the need to develop efficient preventive or management strategies in patients with Influenza virus infections, which shall also include laboratory diagnostics, ultimately aimed at decreasing the risk of unfavorable cardiac outcomes, especially in more vulnerable patients. Although a huge number of putative cardiac biomarkers have been proposed for diagnosing and monitoring cardiac injury, cTn are now universally recognized as the biochemical gold standard [24].

One basic aspect that needs to be clearly emphasized before drawing definitive conclusions on the significance of measuring cTn in patients with Influenza virus infection is

that some drawbacks affect the clinical investigations that have explored this matter so far. First, a limited number of studies have used the novel HS immunoassays, which allow much more accurate detection of a vast array of cardiac injuries, both ischemic and non-ischemic [25]. Specifically, only a total of three studies (total $n = 323$) used HS assays [15,20,22], while the rest of the studies used contemporary sensitive or unspecified immunoassays. Likewise, the cut-offs used in the various investigations are rather heterogeneous, some coincide with the URL, others are considerably higher than the conventional diagnostic thresholds. The sample size and the characteristics of the patient populations also considerably vary among the different studies, so that results generalization appears infeasible. Additional studies would hence be needed before definitive recommendations on cTn testing in patients with Influenza virus infection can be generated. In this perspective, a prospective trial has been registered at the end of the year 2017 in [ClinicalTrials.gov](https://clinicaltrials.gov) (Identifier: NCT03339180; Estimated Study Completion date: December 31, 2021). This investigation is aimed at exploring the values of cardiac injury biomarkers in patients with infection Influenza virus infections, along with their potential prognostic significance in predicting mortality, hospitalization, cardiac ischemia, heart failure, and stroke.

Until the results of this prospective study will become available, some general considerations can be made according to the available published evidence. Taken together, the results of the current scientific literature would lead us to conclude that cTn values elevations are a relatively rare phenomenon in patients with Influenza virus infection, with frequency generally comprised between 0 and 33% and depending on the population studied (i.e., age, sex distribution, presence of cardiovascular complications, and so forth). In patients displaying modest cTn elevations, this phenomenon appears substantially self-limited, mostly transient and reversible, as shown by Han et al. [16], and is more frequent in patients with Influenza A (especially H1N1) virus infections. Nevertheless, in the minority of patients with abrupt appearance of cardiovascular symptoms and concomitantly displaying significant elevations of cTn values, the relative increase of this biomarker reflects the presence of an underlying cardiac injury, that can be either a myocarditis or an acute ischemic episode, thus confirming the role of cTn as essential diagnostic biomarkers and important prognostic predictors. This second aspect has been confirmed in most studies where the association between cTn values and clinical worsening of Influenza virus infection has been addressed, by revealing that enhanced cTn values were more frequently observed in patients with complicated disease [16], in those who developed acute respiratory distress syndrome [12] and cardiac dysfunction [15], as well as in those at higher risk of death [13,19,22]. This is in keeping with the evidence that a continuous release of cTn occurs as a result of a kaleidoscope of primary or secondary cardiac injuries [26], and that the measurable amount of circulating cTn is strongly associated with adverse clinical outcomes and death [27].

As specifically regards Influenza virus infection, there are at least two plausible mechanisms that could justify the pathological increase of cTn concentrations [Fig. 2]. This first encompasses a direct cytotoxic effect of Influenza viruses on

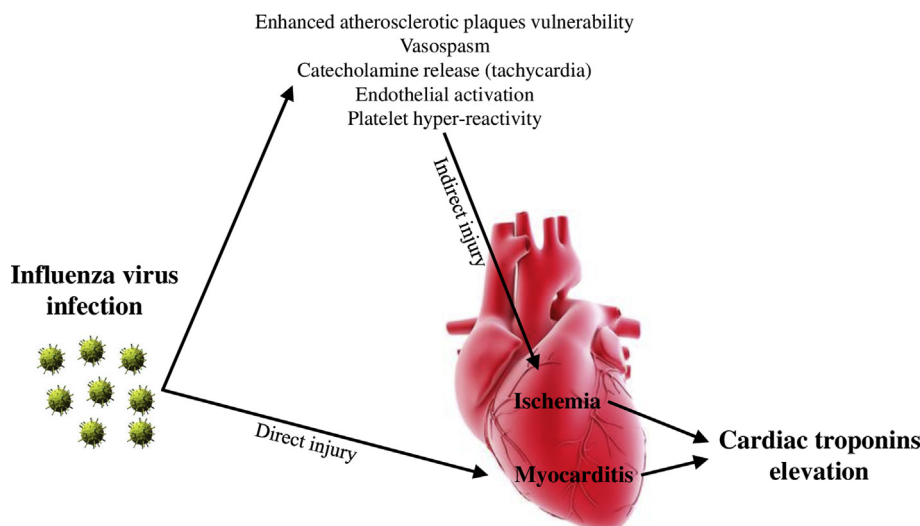


Fig. 2 Potential mechanisms supporting the development of cardiac injury in patients with Influenza virus infection.

myocardiocytes, which evolve towards acute myocarditis [28]. The second mechanism is instead attributable to an unfavorable interplay between Influenza viruses and many biological and metabolic pathways, which finally increases the risk of developing myocardial ischemia. Briefly, Influenza viruses can enhance atherosclerotic plaques vulnerability by generating a selective outgrowth of specific lymphocytes within the microenvironment of human atherosclerotic plaques, thus boosting plaque inflammation and predisposing to the development of complications such as ulceration, up to frank plaque rupture [29]. Influenza viruses can also trigger endothelial activation and platelet hyper-reactivity, two essential events in the pathogenesis of thrombotic disorders. Last but not least, vasospasm and increased catecholamine release (with consequent tachycardia) are frequent in patients with Influenza virus infections, thus enhancing cardiac metabolism [3,30]. Altogether, increased predisposition towards plaque rupture, clot formation and impaired myocardial perfusion compounded by an increased cardiac metabolic demand would contribute to justify the higher risk of developing acute cardiac events in patients with Influenza virus infections [31], which is then mirrored by an obvious increase of cTn values within the circulation [Fig. 2]. Understandably, the risk of measuring diagnostic cTn values is considerably higher in patients with pre-existing coronary artery disease or with other cardiac abnormalities, in whom Influenza virus infections could exacerbate and/or precipitate an already compromised cardiovascular condition [32]. Important evidence has also emerged from the prospective study of Engler et al. [33], who followed up for up to 30 days a total number of 189 subjects undergoing trivalent influenza vaccination. Interestingly, no significant variation of HS-cTnT values could be detected throughout the study period, nor HS-cTnT values exceeded the URL. This implicitly confirms that Influenza vaccine does not produce any meaningful variation of cardiac biomarkers injury and shall hence be considered safe, but also that Influenza vaccination is a valuable strategy for preventing the risk of cardiac injury in patients with Influenza virus infections [4].

In conclusion, we would hence suggest that cTn measurement shall be always considered using HS immunoassays in all patients who develop acute cardiovascular symptoms during Influenza virus infections, as well as in those bearing important comorbidities which may ultimately contribute to worsening their prognosis.

Conflicts of Interest

The authors declare no potential conflicts of interest.

Acknowledgments

Fabian Sanchis-Gomar is supported by a postdoctoral contract granted by “Subprograma Atracció de Talent - Contractes Postdoctorals de la Universitat de València”.

REFERENCES

- [1] Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. *N Engl J Med* 2019;380:171–6.
- [2] Public health weekly reports for NOVEMBER 11, 1932. *Publ Health Rep* 1932;47:2159–89.
- [3] Peretz A, Azrad M, Blum A. Influenza virus and atherosclerosis. *QJM* 2019;112:749–55.
- [4] Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart* 2015;101:1738–47.
- [5] Ruane L, Buckley T, Hoo SYS, Hansen PS, McCormack C, Shaw E, et al. Triggering of acute myocardial infarction by respiratory infection. *Intern Med J* 2017;47:522–9.
- [6] Lippi G, Sanchis-Gomar F. “Ultra-sensitive” cardiac troponins: requirements for effective implementation in clinical practice. *Biochem Med* 2018;28:030501.

- [7] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–69.
- [8] Lippi G, Favaloro EJ, Simundic AM. Biomedical research platforms and their influence on article submissions and journal rankings: an update. *Biochem Med* 2012;22:7–14.
- [9] Greaves K, Oxford JS, Price CP, Clarke GH, Crake T. The prevalence of myocarditis and skeletal muscle injury during acute viral infection in adults: measurement of cardiac troponins I and T in 152 patients with acute influenza infection. *Arch Intern Med* 2003;163:165–8.
- [10] Ison MG, Campbell V, Rembold C, Dent J, Hayden FG. Cardiac findings during uncomplicated acute influenza in ambulatory adults. *Clin Infect Dis* 2005;40:415–22.
- [11] Pecavar B, Nadrah K, Papst L, Cec V, Kotar T, Maticic M, et al. Clinical characteristics of adult patients with influenza-like illness hospitalized in general ward during Influenza A H1N1 pandemic 2009/2010. *Wien Klin Wochenschr* 2011;123:662–7.
- [12] Brown SM, Pittman J, Miller Iii RR, Horton KD, Markewitz B, Hirshberg E, et al. Right and left heart failure in severe H1N1 influenza A infection. *Eur Respir J* 2011;37:112–8.
- [13] Chacko B, Peter JV, Pichamuthu K, Ramakrishna K, Moorthy M, Karthik R, et al. Cardiac manifestations in patients with pandemic (H1N1) 2009 virus infection needing intensive care. *J Crit Care* 2012;27:106.e1–6.
- [14] Song BG, Wi YM, Lee YJ, Hong CK, Chun WJ, Oh JH. Clinical features in adult patients with in-hospital cardiovascular events with confirmed 2009 Influenza A (H1N1) virus infection: comparison with those without in-hospital cardiovascular events. *J Chin Med Assoc* 2012;75:435–41.
- [15] Fagnoul D, Pasquier P, Bodson L, Ortiz JA, Vincent JL, De Backer D. Myocardial dysfunction during H1N1 influenza infection. *J Crit Care* 2013;28:321–7.
- [16] Han J, Mou Y, Yan D, Zhang YT, Jiang TA, Zhang YY, et al. Transient cardiac injury during H7N9 infection. *Eur J Clin Invest* 2015;45:117–25.
- [17] Ludwig A, Lucero-Obusan C, Schirmer P, Winston C, Holodniy M. Acute cardiac injury events \leq 30 days after laboratory-confirmed influenza virus infection among U.S. veterans, 2010–2012. *BMC Cardiovasc Disord* 2015;15:109.
- [18] Wang J, Xu H, Yang X, Zhao D, Liu S, Sun X, et al. Cardiac complications associated with the influenza viruses A subtype H7N9 or pandemic H1N1 in critically ill patients under intensive care. *Braz J Infect Dis* 2017;21:12–8.
- [19] Qian Y, Xie H, Tian R, Lu J, Jin W, Wang R. Clinical significance of early immunological paralysis in patients with severe H1N1 influenza A. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017;29:581–5.
- [20] Ito T, Akamatsu K, Fujita SI, Kanzaki Y, Ukimura A, Hoshiga M. Transient depression of myocardial function after influenza virus infection: a study of echocardiographic tissue imaging. *PLoS One* 2019;14:e0221628.
- [21] Harris JE, Shah PJ, Korimilli V, Win H. Frequency of troponin elevations in patients with influenza infection during the 2017–2018 influenza season. *Int J Cardiol Heart Vasc* 2019;22:145–7.
- [22] Pizzini A, Burkert F, Theurl I, Weiss G, Bellmann-Weiler R. Prognostic impact of high sensitive Troponin T in patients with influenza virus infection: a retrospective analysis. *Heart Lung* 2020;49:105–9.
- [23] Sellers SA, Hagan RS, Hayden FG, Fischer 2nd WA. The hidden burden of influenza: a review of the extra-pulmonary complications of influenza infection. *Influenza Other Respir Viruses* 2017;11:372–93.
- [24] Lippi G, Plebani M. Understanding cardiac troponin biology: all other cardiac biomarkers shall rest in peace? *J Lab Precis Med* 2019;4:9.
- [25] Januzzi Jr JL, Mahler SA, Christenson RH, Rymer J, Newby LK, Body R, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC scientific expert panel. *J Am Coll Cardiol* 2019;73:1059–77.
- [26] Lippi G, Cervellin G, Sanchis-Gomar F. Prognostic value of troponins in patients with or without coronary heart disease: is it dependent on structure and biology? *Heart Lung Circ*; 2020;29:324–30.
- [27] Lippi G, Cervellin G, Sanchis-Gomar F. Predicting mortality with cardiac troponins: recent insights from meta-analyses. *Diagnosis* 2021;8:37–49.
- [28] Rezkalla SH, Kloner RA. Influenza-related viral myocarditis. *Wis Med J* 2010;109:209–13.
- [29] Keller TT, van der Meer JJ, Teeling P, van der Sluijs K, Idu MM, Rimmelzwaan GF, et al. Selective expansion of influenza A virus-specific T cells in symptomatic human carotid artery atherosclerotic plaques. *Stroke* 2008;39:174–9.
- [30] Santos-Gallego CG, Garcia-Ropero A, Badimon JJ. Spark that lights the fire: infection triggers cardiovascular events. *J Am Heart Assoc* 2018;7:e011175.
- [31] Lippi G, Franchini M, Favaloro EJ. Influenza and cardiovascular disease: does swine-origin, 2009 H1N1 flu virus represent a risk factor, an acute trigger, or both? *Semin Thromb Hemost* 2010;36:49–58.
- [32] Estabragh ZR, Mamas MA. The cardiovascular manifestations of influenza: a systematic review. *Int J Cardiol* 2013;167:2397–403.
- [33] Engler RJ, Nelson MR, Collins Jr LC, Spooner C, Hemann BA, Gibbs BT, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. *PLoS One* 2015;10:e0118283.