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Review

The role of invasive coronary physiology in Takotsubo Syndrome

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The pathophysiology of Takotsubo Syndrome has not yet been precisely defined. Different hypotheses have been proposed, including cardiotoxicity due to catecholaminergic hormone release, metabolic disorders, coronary microvascular dysfunction and epicardial coronary artery spasm. Invasive coronary physiology is considered the cornerstone to understand physiological assessment of coronary blood flow in this setting. We have reviewed most important studies in coronary invasive physiology in this field to update the state of the art in TakoTsubo Syndrome.

Keywords

Takotsubo Syndrome; Invasive coronary physiology; Coronary microvascular dysfunction

1. Introduction

Takotsubo Syndrome (TTS) has been described as a clinical syndrome characterized by the presence of left ventricular systolic and diastolic dysfunction in the absence of epicardial coronary obstructive disease. TTS is usually related to a stressful emotional or physical event and it is usually transient [1]. TTS is characterized by the presence of regional Left Ventricular (LV) wall motion abnormalities extending beyond the distribution of a single epicardial coronary artery pattern [2].

LV wall motion abnormality are multipole, including: hypokinesia, akinesia, apical dyskinesia, or apical ballooning with basal hyperkinesia, with a classical image of Japanese octopus trap (Fig. 1A,B) [3].

Clinical manifestations of TTS include oppressive chest pain (in 75% of cases), dyspnea (50% of cases), dizziness (25% of cases) and sometimes generalized weakness or syncope. In most of the cases, TTS shows electrocardiographic abnormalities, slight elevation of serum cardiac biomarkers (Troponin, Brain Natriuretic Peptide o, N-Terminal -proBrain Natriuretic Peptide) [4].

2. Pathophysiology

The pathophysiology of TTS, is ambiguous and has not been previously defined [5]. Different hypotheses have been proposed, including myocardial injury due to catecholaminergic release, metabolic disorders, Coronary Microvascular Dysfunction (CMD) and spasm of epicardial coronary arteries [6]. Stress may be the main promoter of TTS, as reported in a recent paper, 52% of the patients had physical triggering factors, 31% had emotional, and 17% had no identifiable triggering factors [7].

A recent study that has been published by Hiestand *et al.* [8] has demonstrated the existence of anatomical differences between TTS patients and healthy control participants in the limbic system, which plays an important role in controlling emotional processing, and the autonomic nervous system. This supports the neurological hypothesis that brain alterations could lead to cardiac injury in TTS patients [8].

Catecholamines are thought to play a fundamental role in this condition, since elevated serum levels have been found. Adrenaline and norepinephrine, released in stressful scenarios, promote vasospasm of the epicardial vessels and coronary microvasculature, leading to myocardial stunning [9]. The excess of Norepinephrine and neuropeptide Y (which are stored in presynaptic terminals) at the myocardial level after an episode of stress can induce a direct toxic effect, epicardial coronary spam and CMD [10, 11].

3. Coronary microcirculation and invasive coronary physiology

Coronary microcirculation plays a crucial role in the development of TTS, including the coronary arterioles and prearterioles that are responsible for modulating blood flow in response to neuronal, mechanical and metabolic stimuli [11].

The coronary flow and coronary microcirculation parameters usually analyzed include (Fig. 1C):

- Coronary Fractional Flow Reserve (FFR), considered the ratio between mean pressure distal to the stenosis (Pd) and mean aortic pressure (Pa), values below 0.8 mean a significant coronary lesion.

- Coronary Flow Reserve (CFR), considered as the ratio between coronary flow at maximal hyperemia and at baseline conditions. Normal value is above 2.

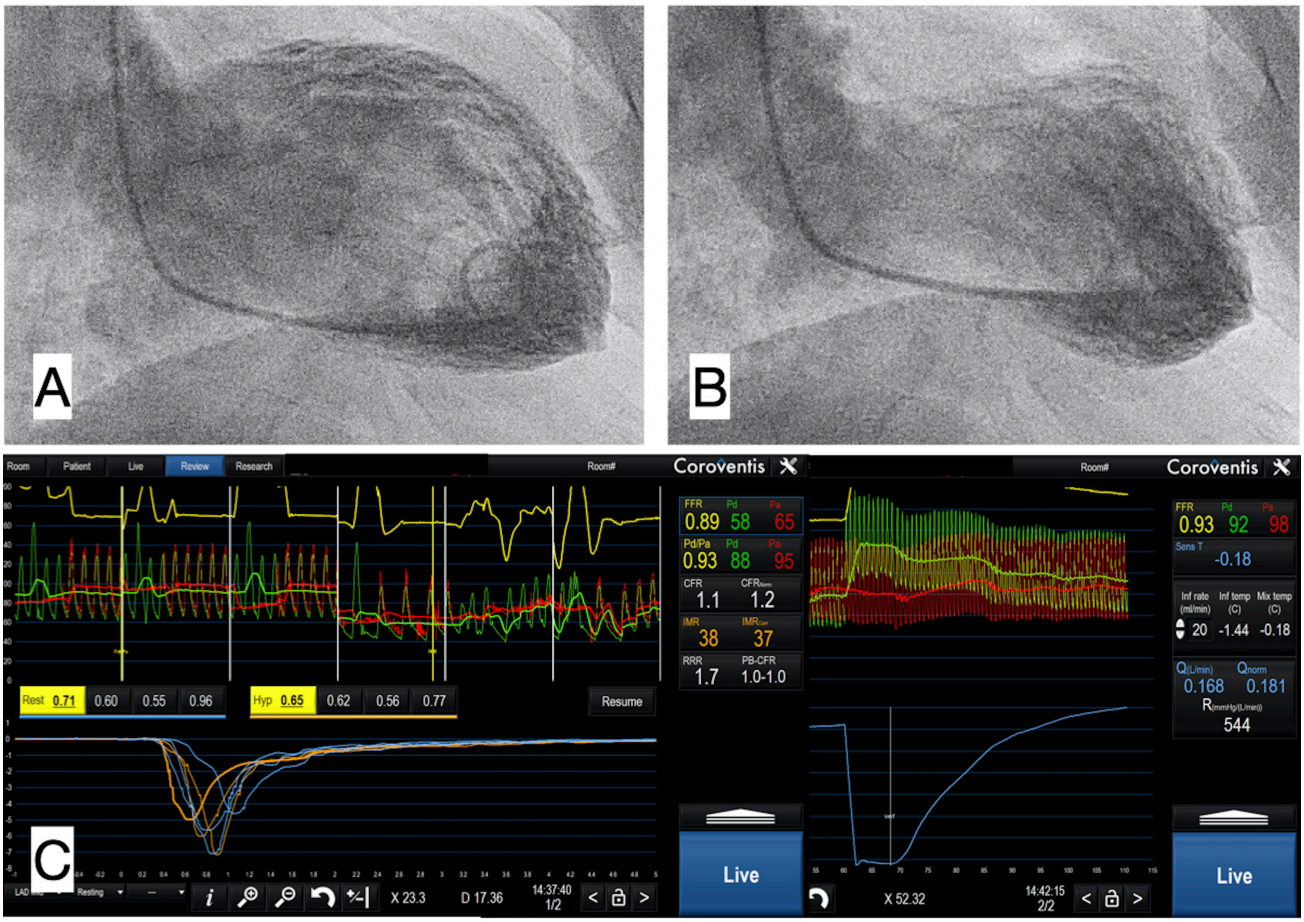

Fig. 1. Ventriculography and coronary physiology in Takotsubo Syndrome. (A) Ventriculography in telediastole. (B) Ventriculography in telesystole, with apical akinesia or apical ballooning. (C) Coronary invasive physiology in Left Anterior Descending coronary artery with Fractional Flow Reserve (FFR) 0.89, Coronary Flow Reserve (CFR) 1.1, Index of Microcirculatory Resistance (IMR) 38, meaning low coronary flow with high microvascular resistances without epicardial coronary lesions.

- Hyperemic Stenosis Resistance (HSR), meaning the ratio between the pressure gradient through the stenosis at maximal hyperemia (Pa-Pd) and mean peak velocity, normal values are considered below 0.8.

- Hyperemic Microvascular Resistance (HMR), defined as the ratio between pressure in the distal part of the artery and mean peak velocity at that point; normal values are <2 [12].

- Index of Microcirculatory Resistance (IMR), is a pressure-temperature sensor guidewire-based measurement, performed during cardiac catheterization, of the minimum microcirculatory resistance in a target coronary artery territory. Normal values are <25.

Other classical parameters included in coronary flow evaluation is Thrombolysis In Myocardial Infarction (TIMI) corrected frame count (cTFC). In this line, Coronary Slow Flow (CSF) pattern, assessed using the cTFC method, have been viewed as a sign of increased coronary microvascular resistance [12]. CSF is generally associated with a severe adrenergic storm and vasoconstrictor mediators release. CSF is usually affected by the clinical characteristics of the patient: smoking, cholesterol, red blood cells, blood glucose levels... [13]. In addition, technical and physiological variables have an impact on TFC, such us force when injecting, use of intracoronary nitrate, high or low heart rate... [14].

A recent study using the cTFC technique showed that cTFC in the left anterior descending artery was significantly higher in TTS than in controls, concluding that this finding could explain the severe apical involvement [15]. However, a previous study found no significant differences in cTFC between 59 women with Takotsubo Syndrome, which does not support the theory of CMD as the only cause of TTS [16].

FFR and IMR in TTS have been evaluated, showing normal FFR but significant CMD associated with high IMR values. On the other hand, a significant drop has been described in HMR values in response to adenosine, that could help to identify the TTS cases most likely to benefit from coronary vasodilator strategies, thus improving overall prognosis for the patients [17].

A recent study has evaluated microcirculatory impairment with IMR in patients with TTS versus patients with ST-segment elevation myocardial infarction (STEMI). CFR, IMR, Thrombolysis in Myocardial Infarction (TIMI) flow grade, TIMI myocardial perfusion grade (TMPG) and cTFC were assessed. The main finding is that microcirculatory function is impaired in TTS patients at the time of presentation. Microvascular dysfunction, as assessed by using IMR, was as high in patients with STS as in those with STEMI, which could mean that both groups may suffer a similar microvascular injury despite the different scenarios [18].

In 2017 a study was carried out to evaluate the presence of CMD in a prospective cohort patients diagnosed with STS. Microvascular resistance indices were invasively measured by placing a pressure guide at the level of the left anterior descending artery, with a transducer distance of 7 to 10 cm from the guide tip. Adenosine was administered to induce maximal hyperemia and subsequently three injections of 1 mL of saline solution at room temperature were administered, confirming the presence of microvascular dysfunction [19].

Bayón *et al.* [20] published the case of a 70-year-old patient with STS, in whom intracoronary pressure and flow were evaluated with a ComboWire XT, at the beginning of the study and post-intracoronary infusion of 300 pg of adenosine. The authors found FFR above 0.8 (not ischemic lesions), low CFR (<2), normal HSR after adenosine infusion and high HMR (>2) in both the left anterior descending and the circumflex arteries, extremely high in Left Anterior Descending (LAD) artery (15.6), with a greater proportional response to adenosine, and this finding may be associated with predominantly apical involvement which is the main finding in TTS.

4. Conclusions

Currently, HMR and IMR are the gold standard for the invasive evaluation of CMD. European guidelines recommend that coronary microvascular dysfunction be diagnosed by measuring CFR or IMR to be more precise than CSF or TFC.

CMD plays a key role in patients with TTS and may occur in 3, 2, or 1 coronary artery distributions (more frequent in LAD) [20]. Coronary physiologic indexes are considered the cornerstone to understand physiological assessment of coronary blood flow in TTS, but more studies will be necessary for a better knowledge of this situation [21].

Author contributions

JB reviewed key information and wrote the manuscript; M-AR contributed the figure on TakoTsubo ventriculography and reviewed the recently published studies; MS-Á, R-AA-S, RO-S and CG-J contributed to this paper by reviewing the main manuscript and the references. All authors made editorial changes in the manuscript. The final manuscript was read and approved by all authors.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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