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Review

Cardiac Nuclear Imaging Findings in Atypical Variants of Takotsubo Cardiomyopathy

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Abstract: Background: In addition to the typical form resembling the classical Japanese octopus trap, atypical variants of Takotsubo cardiomyopathy (TTC) sparing the left ventricular apex have emerged over the years. The aim of this systematic review is to provide a comprehensive overview of the cardiac nuclear imaging findings in atypical variants. Methods: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The literature research was carried out online on the Pubmed, Scopus, Central (Cochrane Library), and Web Of Science databases. Results: A total of 14 articles were ultimately selected. Myocardial perfusion scintigraphy was performed in nine studies, followed by 123I-mIBG scintigraphy, 123I-BMIPP scintigraphy, and 18F-FDG PET. In seven cases, a single cardiac nuclear imaging technique was performed, while in the remaining five and two cases, two and three different imaging modalities were, respectively, used. The most common atypical variant of our selection was the midventricular form, followed by reverse/inverted/basal TTC, with only a single case reported of a focal pattern. Conclusions: As the reason why TTC variants occur is still not clear, a deeper understanding of the current knowledge could be the basis for providing more insights into this fascinating disorder and its uncommon manifestations.

Keywords: takotsubo; 123I-mIBG; 123I-BMIPP; 18F-FDG PET; cardiac nuclear imaging; TTC; myocardial perfusion scintigraphy

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1. Introduction

Takotsubo cardiomyopathy (TTC) was first described in Japanese literature over three decades ago. The name derives from the Japanese term for the typical octopus (tako) trapping pot (tsubo), a fishermen's amphora with a narrow neck and a round bottom, resembling the characteristic end-systolic shape assumed by the left ventricle in the most common variant of the disease [1]. Following the first description, initial reports in the 1990s were mainly from Japan, but have rapidly increased from almost every country since 2000 [2]. TTC has emerged over the years as an important cause of an acute reversible cardiac condition related to transient left ventricular systolic dysfunction with a segmental distribution extending beyond single epicardial coronary artery territories [3], often accompanied by the ballooning of the involved segments, in the absence of significant obstructive coronary artery disease (CAD) [4]. The prevalence of TTC is currently estimated at 1–2% of all patients presenting with symptoms of acute coronary syndrome (ACS) [5,6]. According to the literature data, the incidence is 5.2/100,000 in females and

0.6/100,000 in males [7,8]. Up to 90% of TC patients are women and 80% are over the age of 50 years; the mean age is 67 years, as reported in the International Takotsubo Registry [9]. Although the mechanisms underlying TTC are not fully understood, with several postulated hypotheses existing, including transient multivessel epicardial coronary spasm and microvascular dysfunction [10], a link to sudden stressors and high catecholamine levels has been established [11–13]. The interaction between adrenergic hyperactivation and cardiovascular system response to the peak of catecholamines plays a central role in the pathophysiology of TTC. The large majority of patients diagnosed with TC have experienced either significant emotional, physical, or environmental stress [3,14–16], suggesting how the release of large quantities of norepinephrine from the sympathetic nervous system and epinephrine from the adrenal medulla could be a major mechanism underlying this syndrome [17,18]. Stressors vary widely among reports of TTC cases and include natural disasters to weddings and surprise parties, from surgery and anesthesia to thyrotoxicosis [19] and sepsis, from the postpartum period [20,21] to COVID-19 infection [22], from subarachnoid hemorrhage and stroke to pancreatitis and cholecystitis, from pheochromocytoma to neoplasm and cancer-related therapies, and so on [23]. The reaction to stressors depends on individual factors influencing both catecholamine production and myocyte and microvascular response to sympathetic stimulation [24], with estrogen deficiency, genetic factors, and neurologic and psychiatric disorders being predisposing factors to mental and physical triggers [25–29]. Despite the clinical presentation usually mimicking ACS [30], with patients often presenting with chest pain, followed by dyspnea and syncope [31], having electrocardiographic abnormalities (ST-segment elevation, ST-segment depression, T-wave negative conversion, and QT prolongation) [32] and showing a mild elevation of myocardionecrosis enzyme levels, as well as the marked elevation of brain natriuretic peptide (BNP) and N-terminal pro-BNP [33–36], TTC is formally considered a benign self-limiting state presenting a favorable prognosis [37] and it is generally characterized by a temporary impairment with complete recovery within 3 weeks. However, complications including lethal ventricular arrhythmia, pump failure, outflow tract obstruction, cardiac rupture, and systemic embolization may occur in the acute phase and cause morbidity and mortality. The overlapping of clinical features between TTC and ACS makes particularly critical the early distinction of the two entities, which is of primary importance due to their completely different management. Several diagnostic criteria have been developed following the first proposal by Abe et al. in 2003 [38], but no consensus has yet been reached. The diagnostic criteria issued by the Takotsubo Cardiomyopathy Study Group (TCSG) are commonly followed in Japan [39]. Internationally, the 2008 Revised Mayo Clinic Criteria, based on the presence of transient left ventricle systolic dysfunction, absence of obstructive coronary disease, new electrocardiographic abnormalities or modest elevation in troponin, and absence of pheochromocytoma or myocarditis, are the most widely used [5]. However, certain limitations to the above-mentioned criteria have been recently addressed in the International Takotsubo diagnostic criteria [40]. Specifically, a diagnosis of TTC should not be excluded in the presence of significant CAD, in line with data from the International Takotsubo Registry reporting a rate of coexistence of CAD higher than expected (15.3%) [9]; in the presence of pheochromocytoma, as it can cause TC-like syndrome via catecholamine storm, being a secondary cause of TC [41]; and in the presence of wall motion abnormalities in the distribution of a single coronary artery, considering that rarely a focal subtype of TTC may involve only single coronary artery distribution, typically the anterolateral wall [42]. To predict the probability of diagnosing TTC and to differentiate it from ACS in the acute setting, the Inter Tak Diagnostic Score has been developed [43]. Based on this score, patients with non-ST elevation and a high score (>70 points), reflecting a high probability of TTC, should undergo an echocardiogram to provide an immediate assessment of the regional wall motion abnormalities, to assess right ventricle involvement and to evaluate TTC complications [44–46]. In clinical practice, an early coronary angiography is generally performed without delay within 48 h of the onset of symptoms [47] in patients with acute chest pain, ST-segment elevation, and elevated

cardiac enzymes [48]. Left ventriculography, performed simultaneously with coronary angiography, helps confirm the diagnosis and identify the subtype of TTC [49]. Among non-invasive imaging techniques, both cardiovascular magnetic resonance (CMR) imaging and coronary computed tomography (CT) angiography have been proposed in TTC diagnostic algorithms [50]. In this scenario, cardiac nuclear imaging may represent a further non-invasive diagnostic and prognostic option able to provide additional pathophysiological details thanks to its functional nature. In a recent systematic review, Nayar et al. summarized the current literature, from perfusion and metabolic studies to sympathetic innervation imaging, underlining their role in improving diagnostic accuracy, providing prognostic information, and appreciating TTC pathophysiology [51]. However, at present, cardiac nuclear imaging is not included in the main diagnostic criteria [39]. To date, the term 'takotsubo' is widely used in recognition of Sato et al., who first described it in 1990 [52,53], but a consensus has not been reached, leading to variable nomenclature in the literature including acute stress-induced cardiomyopathy, broken-heart syndrome [54], apical ballooning syndrome, or ampulla cardiomyopathy [55], with no term properly describing the heterogeneous ventricular appearance of this syndrome [56]. The typical form, accounting for 80% of all cases, affects the left ventricle apex with end-systolic hypercontraction and the narrowing of basal segments associated with akinesia of the mid and apical segments, resulting in the apical ballooning form of the classical Japanese octopus trap [57]. However, atypical forms of TTC sparing the left ventricular apex have been described in the literature [58,59]. The midventricular form with a hawk's beak appearance [60,61], often referred to as "midventricular ballooning syndrome" is the most common atypical form (4–40%), presenting with midventricular dilation and akinesia in end-systole and hyperkinetic basal and apical segments. The basal or reverse or inverted type, showing basal dyskinesia with midventricular and apical sparing, as well as the focal type, represent less common atypical variants, occurring in 2.2% and 1.5% of subjects, respectively [9,62]. Right ventricle-isolated involvement and biventricular forms have also been observed [63,64]. The prevalence of such atypical forms has previously been considered rare, but the reported number of TTC variants has continuously increased during recent years [65–69], so that the expression "transient left ventricular dysfunction syndrome" (TLVDS), not including any reference to the specific shape taken by the left ventricle, has been proposed as a new and more appropriate definition for TTC [70]. Dealing with the uncommon presentations of a still not fully understood disorder represents a further challenge. To our knowledge, there are only a few reports involving cardiac nuclear imaging in atypical variants of TTC [71,72]. The aim of this systematic review was to provide a comprehensive overview of the cardiac nuclear imaging findings in atypical variants of TTC by using a systematic approach to identify and collect published studies on this topic. A focus was put on the potential contribution of nuclear medicine for a more complete understanding of the atypical variants of this fascinating disorder.

2. Materials and Methods

2.1. Search Strategy and Study Selection

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [73]. The literature research was carried out online on Pubmed, Scopus, Central (Cochrane Library), and Web Of Science databases with a search strategy based on the following keywords: "Reverse" OR "Inverted" OR "Basal" OR "Midventricular" OR "Focal" OR "Atypical Takotsubo" AND "Nuclear Medicine". The search included all papers published until May 2023. English language was mandatory for inclusion. Eligible articles had to focus on the role of cardiac nuclear imaging in patients with atypical variants of TTC. Publications concerning the typical apical form were excluded, as well as reviews, animal studies, and articles not performing nuclear imaging studies. In addition to retrospective analysis and prospective studies, case reports, case series, letters to the editor, and interesting images were included. The reference lists of suitable studies were carefully checked to identify any additional relevant literature.

2.2. Data Extraction and Methodological Quality Assessment

Data extraction included authors, location, year of publication, type of study, sample size, gender and age, type of atypical variant of TTC, type of nuclear medicine study, and relevance of imaging findings in the acute phase and during follow-up. The methodological quality assessment was performed through the Critical Appraisal Skills Programme (CASP) [74]. Both data extraction and critical appraisal were independently performed by two reviewers. Disagreements and discrepancies were resolved by unanimous approval after discussion among researchers.

3. Results

3.1. Search Results

A total of 104 articles were found and thus screened by examining each abstract in order to identify suitable studies. A total of 14 articles were ultimately selected for the qualitative analysis of this systematic review. The detailed study selection flow chart, showing the search strategy and the applied selection criteria, is presented in Figure 1.

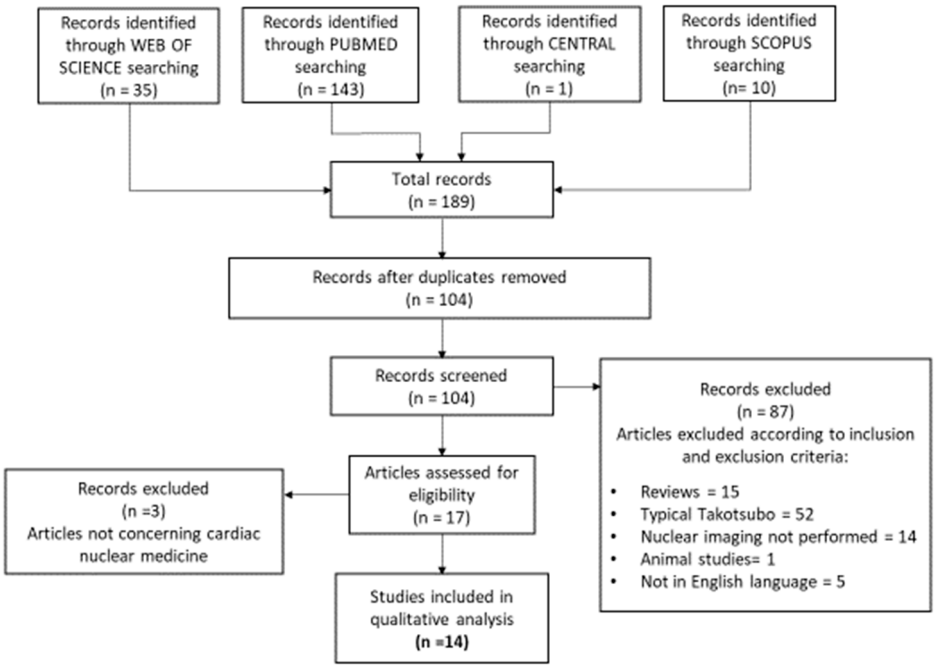

Figure 1. PRISMA flow chart.

3.2. Methodological Quality

The critical appraisal only involved the retrospective studies by Kurowski et al. [70] and Cimarelli et al. [71] and the prospective study by Miyajima and colleagues [75] (Figure 2). Case reports and case series were not considered as a part of this process. All the analyzed studies satisfied at least 8 of the 11 domains but showed high risk in two domains. One of the major concerns with the selected papers was represented by the lack of a reference standard, as the diagnosis of TTC is based on specific diagnostic algorithms rather than a single test. In addition, the absence of an adequate follow-up limited the evaluation of patients' outcomes in one study. Finally, it was found there was a level of high concern of the applicability in evaluating the possibilities of the application of the reported results. However, cumulatively, the quality appraisal result was quite good.

	1. Was there a clear question for the study to address?	2. Was there a comparison with an appropriate reference standard?	3. Did all patients get the diagnostic test and reference standard?	4. Could the results of the test have been influenced by the results of the reference standard?	5. Is the disease status of the tested population clearly described?	6. Were the methods for performing the test described in sufficient detail?	7. What are the results?	8. How sure are we about the results? Consequences and cost of alternatives performed?	9. Can the results be applied to your patients/the population of interest?	10. Can the test be applied to your patient or population of interest?	11. Were all outcomes important to the individual or population considered?	12. What would be the impact of using this test on your patients/population?
Kurowski et al. 2007	☺	☺	☺	☹	☺	☺	☺	?	☹	☺	☺	It may help in the identification of atypical variants through the correlation between location of perfusion/metabolism defects and wall motion abnormalities.
Cimarelli et al. 2010	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☺	It may underline the role of nuclear imaging in the setting of patho-physiological mechanisms of TTC
Miyajima et al. 2022	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☺	It may indicate a reversible disorder of the myocardial cell membrane, mitochondria, and microcirculation.

☺ Low risk; ? Unknown; ☹ High risk

Figure 2. CASP diagnostic checklist: tabular representation of quality assessment results [70,71,75].

3.3. Analysis of the Evidence

The 14 selected papers were published from 2004 to 2021. Most of the studies were conducted by authors from Japan (n = 7), followed by researchers from France (n = 3) and Italy (n = 2), with the remaining two studies performed in the USA and in Germany. Only two retrospective studies and one prospective study were found according to the selection criteria. The majority of the selected studies were case reports involving one or two patients. Letters to the editor (n = 3) and interesting images (n = 2) were also included. The total number of patients was 37. It is worth specifying that this number is not the sum of the subjects involved in the selected papers but represents the result of a further selection carefully performed for each single publication to include only patients with atypical variants of TTC, since four studies also included subjects with the typical apical form. For completeness, we should also underline that the study by Kurowski et al. [70] does not specify whether all 13 of their subjects with atypical variants were submitted to cardiac nuclear imaging, so the total number of 37 could be slightly overstated. Subjects were mostly women (30 females, 7 males). As concerning cardiac nuclear imaging, myocardial perfusion scintigraphy was performed in nine studies, specifically with technetium-99m (99mTc) sestamibi in four papers, with thallium-201 (201Tl) in an additional four studies and with 201Tl or 99mTc-tetrofosmin in the remaining one, followed by I-123-meta-iodobenzyl-guanidine (123I-mIBG) myocardial scintigraphy (n = 7), I-123-beta-metyl-iodophenyl pentadecanoic acid (123I-BMIPP) myocardial scintigraphy (n = 4), and fluorine-18-fluoro-2-deoxyglucose (18F-FDG) positron emission tomography (PET) (n = 3). In most cases (n = 7), a single cardiac nuclear imaging technique was performed, while in the remaining five and two studies, two and three different imaging modalities were, respectively, used. According to the literature data, the most common atypical variant of our selection of studies was the midventricular form (n = 8), followed by reverse/inverted/basal TTC (n = 5), with only a single case report of a focal pattern. The scintigraphic follow-up data concerning atypical variants are available in a minority of publications (n = 3), while in the case report by Cadeddu et al. [76], 123I-mIBG scintigraphy was not performed in the acute phase. The main characteristics of the included studies are reported in Table 1. The cardiac nuclear imaging findings of the selected papers for each type of atypical variant of TTC are described in detail in the following paragraphs.

3.3.1. Cardiac Nuclear Imaging Findings in Midventricular TTC

In 2008, Cimarelli and colleagues [72], analyzed imaging patterns obtained with 99mTc-tetrofosmin gated-single photon emission computed tomography (G-SPECT), 123I-mIBG SPECT, and 18F-FDG gated-positron emission tomography (G-PET) of an 83-year-old

woman with typical TTC and a 67-year-old woman with transient midventricular ballooning. In the patient with the atypical variant of TTC, despite the myocardial perfusion images revealing no defects, the analysis of the left ventricular motion and thickness showed severe midventricular hypokinesia associated with a decreased left ventricular ejection fraction (LVEF) measured by G-SPECT. Moreover, the authors revealed a similar pattern of 123I-mIBG and 18F-FDG uptake, with defects related to left ventricular dysfunction. Following this case report, a retrospective study involving a total of 18 patients, of whom 5 subjects had midventricular TTC, was published in 2009 [71]. Myocardial perfusion imaging with 99mTc-tetrofosmin or 201-Tl was performed on three out of five subjects in the sub-acute phase and revealed the absence of perfusion defects, associated with a severe midventricular hypokinesis with preserved apical and basal function. 123I-mIBG SPECT and 18F-FDG G-PET were performed in one and in all five patients, respectively. Hypocontractile but normally perfused segments were characterized by a severe decrease in both 123I-mIBG and 18F-FDG uptake, with a large topographic overlapping of the metabolic defects and innervation abnormalities on the qualitative analysis. Previously, in 2007, Kurowski and coworkers [70] retrospectively analyzed 35 patients with TLVDS, of whom 13 had atypical midventricular TTC. The myocardial perfusion 99mTc-sestamibi scintigraphy and 18F-FDG PET studies showed a strong correlation between the location of the wall motion abnormality and myocardial perfusion/metabolism defects. In particular, myocardial glucose metabolism was revealed to be affected to a greater extent than perfusion, leading to an inverse mismatch typical for the appearance of postischemic stunned myocardium. A case of transient midventricular akinesia in a 67-year-old woman without a history of heart disease was reported in 2008 by Moriya et al. [77]. During the acute phase, decreased uptake was seen in the 123I-BMIPP myocardial scintigraphy. The main finding in the acute phase was the discrepancy of the uptake between the mid region and apex, which reduced during the course. On the other hand, the decreased uptake revealed on the 123I-mIBG scintigraphy in the mid portion during the acute phase persisted through 3 and 6 months later. Similarly, the washout map showed an increased washout in the mid to basal portion of the inferior and lateral wall during the acute phase and increased the washout in the mid portion of the anterolateral wall in images taken 3 and 6 months later, suggesting how the abnormal findings of the 123I-mIBG persisted for 6 months even though the left ventricle contraction was recovered. The above-described findings concerning 123I-BMIPP scintigraphy are in line with a previous case report of a 51-year-old Japanese man published in 2007 by Yoshikawa and colleagues [78], who revealed a decreased uptake in the mid ventricle corresponding to the midventricular akinetic region, which normalized at 4 months after discharge. 99mTc-sestamibi scintigraphy, also performed by the authors on the fifth day, showed no perfusion defects. Similarly, normal 201Tl uptake was revealed on early images performed on the third day of admission in an 87-year-old woman diagnosed with a midventricular variant of TTC, as reported by Yoshida and coworkers [79] a year later. After a coronary angiogram showed no organic stenosis, a ventriculogram revealed akinesis in the middle portion of the left ventricle and transthoracic echocardiography (TTE) confirmed the abovementioned finding, 201Tl scintigraphy and 123I-mIBG scintigraphy were performed to exclude a possible previous myocardial injury by Nagai et al. [80], who published an interesting image in 2014. The mismatch images obtained by subtracting the 201Tl images showing no defects from the corresponding 123-I BMIPP images showing metabolic abnormalities revealed a ring-shaped defect on the polar maps in this 74-year-old woman with mid-ventricular ballooning syndrome. In 2012, Arao et al. [81] also reported a “doughnut-like” circular uptake reduction on bull’s eye imaging in 123I-mIBG scintigraphy performed on the sixth day in an 83-year-old woman referred to their institution. The involved area coincided with the ballooning region demonstrated through left ventriculography but not with any epicardial coronary artery territory.

3.3.2. Cardiac Nuclear Imaging Findings in Basal/Inverted/Reverse TTC

Three out of five papers concerning basal/inverted/reverse TTC were performed using 123I-mIBG scintigraphy as a single cardiac nuclear imaging technique. In 2011, Cadeddu and colleagues [76] published a rare case of dobutamine-induced inverted TTC, which occurred with an atypical presentation including no chest pain, no ECG abnormalities, and a lack of increase in cardiac troponin. A 48-year-old female patient was referred to their echo laboratory due to a long history of atypical precordial chest pain. During a dobutamine/atropine stress echocardiogram, hypokinesia of the mid-basal anterior wall was noted and the test was interrupted. The recovery images showed a progressive worsening of the kinetic pattern with akinesia of all the left ventricular mid-basal segments and severe impairment of the global systolic function (LVEF = 25%). 123I-mIBG myocardial scintigraphy performed two months later showed decreased uptake in the whole left ventricle with increased washout in late images. A few years later, an interesting image by Humbert et al. [82] highlighted the dual role of 123I-mIBG scintigraphy in TTC through the case of a 41-year-old woman showing ischemic stroke and cardiogenic pulmonary edema a few hours after hysterectomy due to endometriosis. TTE showed a low LVEF at 25% with thrombi in the left ventricle. CMR performed a few days later revealed apical hyperkinesis and basal hypokinesis, as well as no late gadolinium enhancement. 123I-mIBG scintigraphy confirmed the presence of the acute dysfunction of the myocardial sympathetic nerve endings and revealed decreased uptake in the hypokinetic basal segments, sparing the apex, suggesting an atypical pattern of TTC. The whole-body planar scintigraphy performed 24 h after injection showed a high uptake of the right adrenal mass consistent with the presence of a pheochromocytoma, a possible endogenous cause of adrenergic stress related cardiomyopathy. In this case, 123I-mIBG allowed for the final diagnosis of inverted stress-related cardiomyopathy secondary to pheochromocytoma. Following this paper, a year later, Ceccacci and colleagues [83] reported the case of a 40-year-old woman admitted to the Emergency Department for syncope associated with severe oppressive pain in the epigastric region. According to the Mayo Clinic criteria, the absence of coronary lesions, the presence of dyskinesia of the basal and middle segments, as well as the absence of myocarditis as confirmed by CMR, strongly suggested the diagnosis of inverted takotsubo cardiomyopathy which was confirmed through 123I-mIBG scintigraphy revealing increased adrenergic receptor activity in the apex, with simultaneous reduction in the basal region (See Figure 3). Myocardial scintigraphy with 99mTc-sestamibi was performed as a single cardiac nuclear imaging modality to assess the left ventricular perfusion in the remaining two publications. A fixed midventricular and basal circumferential area of hypoperfusion and hypokinesis with preservation of the ventricular apex was revealed during a rest–stress dipyridamole Tc-99m sestamibi myocardial perfusion G-SPECT by Davis and coworkers [84] in a 49-year-old black male admitted to the intensive care unit with acute respiratory failure with anoxic encephalopathy and elevated cardiac biomarkers. In this case, as the anatomical distribution of the specific perfusion defects did not appear to represent obstructive epicardial coronary pathology, immediate coronary angiography was not performed and a final diagnosis of atypical stress-induced cardiomyopathy was made. In a recent study published in 2021, Miyajima et al. [75] prospectively enrolled 20 patients with typical TTC and 8 patients (6 females, 2 males) with reverse TTC and assessed the minimum percentage uptake (min-%-uptake), extent score (ES), and summed rest score (SRS) at acute and chronic phases through myocardial perfusion scintigraphy with 99mTc-sestamibi. In the group of subjects with reverse TTC, the imaging procedure was performed within a few days after admission in the acute phase and approximately one month after admission in the chronic phase. The analysis revealed that the min-%-uptake, ES, and SRS were mild to moderately reduced in the acute phase and were normalized with progression from acute to chronic phase in both TTC groups, suggesting how reversible disorders such as microcirculation, myocardial cell membrane, and mitochondria may be involved in the pathophysiology.

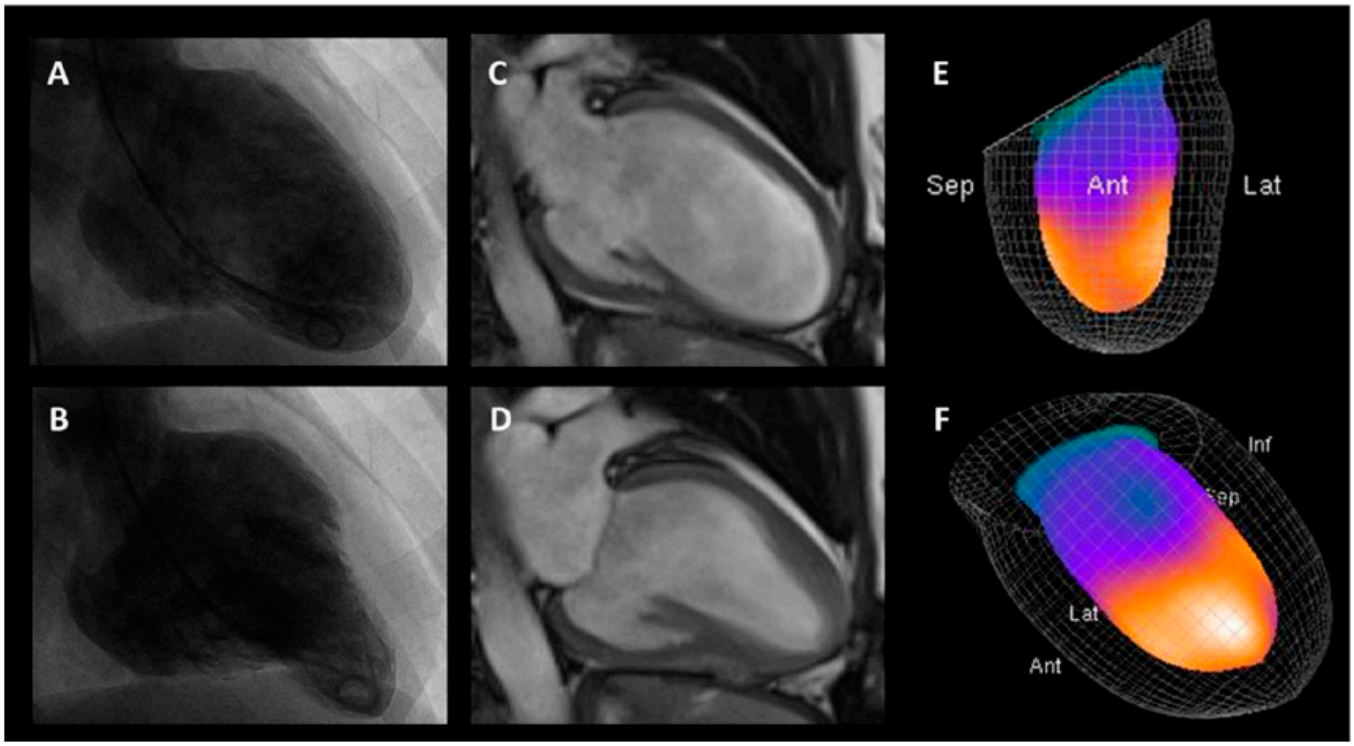

Figure 3. A case of inverted/reverse/basal TTC. Left ventriculography ((**A**): diastolic phase; ((**B**): systolic phase) and cardiac magnetic resonance imaging ((**C**): diastolic phase; (**D**): systolic phase) show a depressed systolic function with dyskinesia of the basal and middle segments (Figure: (**A**–**D**)) and hyperkinesia of apex and para-apical areas (Figure: (**A**–**D**)). Figure (**E**,**F**) show an increased adrenergic receptor activity in the apical side of the left ventricle, with simultaneous reduction in the basal region to the 123I-mIBG scintigraphy [83].

3.3.3. Cardiac Nuclear Imaging Findings in Focal TTC

In 2004, the case of a 64-year-old man was published by Suzuki et al. [85]. He was a heavy drinker admitted due to hypokalemia-related myopathy and suffered a cardiopulmonary arrest lasting approximately 5 min on the fifth hospital day. 201Tl perfusion scintigraphy, performed on the tenth day, showed no perfusion defects, while 123I-BMIPP scintigraphy, performed on the fourteenth hospital day, revealed decreased uptake in the anterior and septal regions of the left ventricle in agreement with the anteroseptal area of left ventricular wall motion abnormality. Cardiac nuclear imaging contributed to formulating the possible diagnosis of an atypical focal form of TTC.

Table 1. Characteristics of included studies.

Source, Year, Location, Type of Study	Number of Patients, Sex, Age	TTC Variant	Cardiac Nuclear Imaging Technique	Time from Acute Event to First Imaging/Follow Up	Tracer Uptake in Involved Segments during the Acute Phase/at Follow-Up
Suzuki et al., 2004, Japan, case report [85]	1 M, 64 y	focal	- 201Tl SPECT - 123I-BMIPP SPECT	- 10 days/NP - 14 days/NP	- normal/NP - reduced/NP
Yoshikawa et al., 2007, Japan, letter to the editor [78]	1 M, 51 y	midventricular	- 99mTc-sestamibi-SPECT - 123I-BMIPP SPECT	- 5 days/NP - 5 days/4 months	- normal/NP - reduced/normalized
Kurowski et al., 2007, Germany, retrospective study [70]	12 F and 1 M, 70.4 y ± 10.2 y	midventricular	- 99mTc-sestamibi SPECT - 18F-FDG PET	2 to 6 days (mean 4)/NP	- mildly reduced/NP - severely reduced/NP
Yoshida et al., 2009, Japan, letter to the editor [79]	1 F, 87 y	midventricular	201Tl SPECT	3 days/NP	normal/NP
Moriya et al., 2009, Japan, case report [77]	1 F, 67 y	midventricular	- 123I-BMIPP SPECT - 123I-mIBG SPECT	- NA/3 and 6 months - NA/3 and 6 months	- reduced/normalized - reduced/reduced
Cimarelli et al., 2008, France, case report [72]	1 F, 67 y	midventricular	- 99mTc-tetrofosmin G-SPECT - 123I-mIBG SPECT - 18F-FDG G-PET	- 4 days/NP - 6 days/NP - 8 days/NP	- normal/NP - absent/NP - markedly reduced/NP
Cimarelli et al., 2010, France, retrospective study [71]	4 F and 1 M, median age 67 y (range: 13–87 y) *	midventricular	- 99mTc-tetrofosmin/201Tl G-SPECT (n = 3) - 123I-mIBG SPECT (n = 1) - 18F-FDG G-PET (n = 5)	- 10.4 days (range: 5–15) * /NP - 11.6 days (range: 4–20) * /NA - 8.9 days (range: 3–20) * /NA	- normal/NP - reduced/NA - reduced/NA

Table 1. *Cont.*

Source, Year, Location, Type of Study	Number of Patients, Sex, Age	TTC Variant	Cardiac Nuclear Imaging Technique	Time from Acute Event to First Imaging/Follow Up	Tracer Uptake in Involved Segments during the Acute Phase/at Follow-Up
Davis et al., 2009, USA, case report [84]	1 M, 49 y	reverse/inverted/basal	99mTc-sestamibi SPECT	NA/NP	reduced/NP
Cadeddu et al., 2011, Italy, case report [76]	1 F, 48 y	reverse/inverted/basal	123I-mIBG SPECT	NP/2 months	NP/reduced
Arao et al., 2013, Japan, letter to the editor [81]	1 F, 83 y	midventricular	123I-mIBG SPECT	6 days/NP	reduced/NP
Nagai et al., 2014, Japan, image focus [80]	1 F, 74 y	midventricular	- 201Tl SPECT - 123I-BMIPP SPECT	NA/NP	- normal/NP - reduced/NP
Humbert et al., 2015, France, interesting image [82]	1 F, 41 y	reverse/inverted/basal TTC secondary to pheochromocytoma	123I-mIBG SPECT	NA/NP	reduced/NP
Ceccacci et al., 2016, Italy, case report [83]	1 F, 40 y	reverse/inverted/basal	123I-mIBG SPECT	NA/NP	reduced/NP
Miyajima et al., 2022, Japan, prospective study [75]	6 F and 2 M, 58y [44–83]	reverse/inverted/basal	99mTc-sestamibi SPECT	3.0 [2.0–3.0] days/35 [24–46] days	mild to moderately reduced/normalized

Abbreviations: y: years; F: female; M: male; NA: not applicable; NP: not performed; *: data reflecting the total cohort including patients with typical TTC.

4. Discussion and Limitations

Different studies have shown a decreased tracer uptake at myocardial perfusion imaging during the acute phase of TTC, and its gradual improvement in the subacute and chronic phases [86,87]. However, most literature data show normal myocardial perfusion during the subacute phase of TTC in hypo-contractile ventricular segments reflecting preserved coronary blood flow and blood flow reserve [88–90]. The association between normal perfusion and reduced metabolism is commonly known as inverse flow–metabolism mismatch and it is considered the metabolic state of stunned myocardium [91]. According to these findings, stunned myocardium mediated by catecholamine oversecretion seems to play a crucial role in TTC, with transient coronary microvascular dysfunction representing a potentially associated phenomenon secondary to acute catecholamine release, rather than the primary causative mechanism of the disease. Cardiac autonomic innervation is a complex system. To preserve homeostasis, the stress-activated post-ganglionic sympathetic nerve releases norepinephrine into the synaptic cleft, producing a wide range of cardiac effects on the heart rate, blood pressure, and contractility through the interaction with a post-synaptic adrenergic receptor (AR). However, during the acute phase of TTC, high circulating levels of epinephrine and norepinephrine may cause catecholamine toxicity in myocardial cells. Animal studies have suggested that acute catecholamine overload may lead to a stunning of the myocardium [92] and have a negative inotropic action with apical ballooning in rats [93], due to a shift to an inhibitory signal mediated by ß2 AR, particularly abundant in the apical region [94]. In addition to the highest density of ß-AR, the mammalian left ventricular apex shows the lowest density of sympathetic innervation, a combination making it particularly sensitive and vulnerable to exaggerated sympathetic stimulation than the mid and basal segments [95,96]. The description of the variant forms of TTC sparing the apex might be explained by the interindividual differences in the distribution of sympathetic receptors in the left ventricle, as speculated by Kurowsky et al. [70], as well as by Cimarelli and coworkers in the case series published in 2008 and a year later in a retrospective study [71,72]. However, as a case of both typical and atypical TTC occurring in the same patient at different periods was reported [97], probably, the pathogenesis of TTC variants cannot be explained only by the individual distribution of AR in the myocardium [81]. The reason atypical variants occur and whether they resemble basic pathophysiology with TTC simply affecting different left ventricular regions still remains a matter of speculation. In this background, cardiac nuclear imaging may improve the current knowledge of the atypical manifestations of this fascinating and still mysterious disease.

Given the hypothesis of enhanced catecholamine release secondary to exaggerated sympathetic stimulation as the central causative mechanism of TTC, 123I-mIBG scintigraphy seems to be the most specific diagnostic imaging tool [98,99]. 123I-mIBG, a structural analog of norepinephrine reflecting sympathetic neuron integrity and function, represents an extremely useful imaging tool for detecting abnormalities in the myocardial adrenergic

nervous system and for studying the causes and effects of cardiac sympathetic hyperactivity [100–102]. In patients with TTC, the increased levels of plasma catecholamines inhibit neuronal norepinephrine uptake by presynaptic sympathetic endings [103], resulting in reduced signal in the involved segments of the left ventricle on 123I-mIBG scintigraphy [99,104]. In 2005, Ito et al. [89] observed the same discrepancies between long-chain fatty acid uptake assessed through 123I-BMIPP scintigraphy and cardiac innervation on 123I-mIBG scintigraphy, suggesting the existence of sympathetic nerve control on cardiac metabolism. Similarly, a large correlation between the location and extent of 123I-mIBG defects and reduced glucose metabolism is reported in the literature, suggesting that catecholamine-mediated myocardial insulin resistance as well as the inhibited intracellular translocation of glucose transporters (GLUT-4) by calcium overload may be responsible for the transient reduced 18F-FDG uptake in the hypokinetic areas [105,106]. In addition, catecholamines exert a large vasoconstrictor effect potentially causing transient multivessel epicardial coronary spasm and microvascular dysfunction [107–111].

Cardiac nuclear imaging findings in atypical variants of TTC reflect literature data published for the typical apical form, but with different distribution patterns of uptake defects. In particular, the analysis of the selected papers showed normal perfusion in most publications, with a mild reduction reported only in a minority of papers [70–84], always followed by complete normalization on follow-up studies when performed [75–77]. Perfusion G-SPECT confirmed the presence of motion and thickness abnormalities, associated with a reduction in LVEF during the acute phase, in accordance with echocardiographic findings [72]. Concerning the evaluation of sympathetic innervation, 123I-mIBG scintigraphy always revealed a marked reduction in tracer uptake in the involved area during the acute phase [72], reflecting the central role of abnormal myocardial adrenergic nervous system activation in the pathogenesis of the disease and non-invasively contributing to the final diagnosis of atypical TTC [81,83]. Moreover, in one case, it was extremely useful in identifying a pheochromocytoma as a secondary cause of TLVDS [82]. As discussed above, sympathetic nervous system dysfunction may be the mechanism underlying the metabolic alterations revealed through both 123I-BMIPP scintigraphy [80] and 18F-FDG PET [70–72]. The transient nature of all these defects is always confirmed in follow-up studies [78], with a possible delay in the recovery of sympathetic function with respect to metabolic defects [76,77]. However, these data are scarce and difficult to compare as the time occurring from the onset of symptoms to cardiac nuclear imaging in both acute phase and during follow-up is extremely variable.

A mention of some additional limitations and drawbacks is needed. First of all, it is worth highlighting that the number of selected studies is quite limited. Both the rare occurrence of uncommon forms of TTC and the non-inclusion of cardiac nuclear imaging in the diagnostic pathway could be possible explanations for the low number of publications on this topic. Moreover, one of the major concerns in the analyzed literature is represented by the type of published papers, as the vast majority of them are single case reports or case series involving no more than two patients. We can speculate that the paucity of both retrospective analyses and prospective studies concerning cardiac nuclear imaging in TTC in general and atypical TTC variants in particular may represent the main obstacle preventing it from being included in the current diagnostic algorithms. An additional non-negligible limitation of most papers is represented by the lack of follow-up imaging, particularly useful for corroborating the transient nature of nuclear imaging findings.

5. Conclusions

Following the first reports from Japan, interest in TTC has spread worldwide, fueled by its fascinating and still not fully understood pathogenesis. Over the years, cardiac nuclear imaging has not only provided complementary diagnostic and prognostic information in a non-invasive manner, but has contributed to the pathophysiological understanding of TTC by assessing myocardial perfusion, innervation abnormalities as well as metabolic alterations in both the acute and chronic phases of the disease. According to the available

data, it is possible to suppose that typical and atypical TTC resemble basic pathophysiology, so that the disease should no longer be regarded as an apical ballooning syndrome, but rather a transient left ventricular dysfunction showing different phenotypes. The present review could be the starting point for systematically investigating both the diagnostic role and the prognostic contribution of cardiac nuclear imaging in uncommon TTC forms. Moreover, since the reason why atypical variants occur is still not clear, we believe that a deep understanding of the current knowledge on this topic may be the basis for the development of cardiac nuclear imaging tracers with more and more specific targets in the myocardium, able to provide more insights into the less common manifestations of this fascinating disorder.

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References

1. Fernández-Pérez, G.C.; Aguilar-Arjona, J.A.; de la Fuente, G.T.; Samartín, M.; Ghioldi, A.; Arias, J.C.; Sánchez-González, J. Takotsubo cardiomyopathy: Assessment with cardiac MRI. *Am. J. Roentgenol.* **2010**, *195*, W139–W145. [CrossRef] [PubMed]
2. Sharkey, S.W.; Lesser, J.R.; Zenovich, A.G.; Maron, M.S.; Lindberg, J.; Longe, T.F.; Maron, B.J. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* **2005**, *111*, 472–479. [CrossRef] [PubMed]
3. Ghadri, J.-R.; Wittstein, I.S.; Prasad, A.; Sharkey, S.; Dote, K.; Akashi, Y.J.; Cammann, V.L.; Crea, F.; Galiuto, L.; Desmet, W.; et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur. Heart J.* **2018**, *39*, 2032–2046. [CrossRef] [PubMed]
4. Murthy, A.; Arora, J.; Singh, A.; Gedela, M.; Karnati, P.; Nappi, A. Takotsubo Cardiomyopathy: Typical and Atypical Variants, A Two-Year Retrospective Cohort Study. *Cardiol. Res.* **2014**, *5*, 139–144. [CrossRef] [PubMed]
5. Prasad, A.; Lerman, A.; Rihal, C.S. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. *Am. Heart J.* **2008**, *155*, 408–417. [CrossRef]
6. Tsuchihashi, K.; Ueshima, K.; Uchida, T.; Oh-Mura, N.; Kimura, K.; Owa, M.; Yoshiyama, M.; Miyazaki, S.; Haze, K.; Ogawa, H.; et al. Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. *J. Am. Coll. Cardiol.* **2001**, *38*, 11–18. [CrossRef]
7. Agarwal, S.; Bean, M.G.; Hata, J.S.; Castresana, M.R. Perioperative Takotsubo Cardiomyopathy: A Systematic Review of Published Cases. *Semin. Cardiothorac. Vasc. Anesthesia* **2017**, *21*, 277–290. [CrossRef]
8. Natale, E.; Mistrulli, R. Takotsubo syndrome: More frequent in women, more dangerous in men. *Eur. Heart J. Suppl.* **2023**, *25*, B119–B122. [CrossRef]
9. Templin, C.; Ghadri, J.R.; Diekmann, J.; Napp, L.C.; Bataiosu, D.R.; Jaguszewski, M.; Cammann, V.L.; Sarcon, A.; Geyer, V.; Neumann, C.A.; et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N. Engl. J. Med.* **2015**, *373*, 929–938. [CrossRef]
10. Rivero, F.; Cuesta, J.; García-Guimaraes, M.; Bastante, T.; Alvarado, T.; Antuña, P.; Alfonso, F. Time-Related Microcirculatory Dysfunction in Patients With Takotsubo Cardiomyopathy. *JAMA Cardiol.* **2017**, *2*, 699–700. [CrossRef]
11. Amin, H.Z.; Pradipta, A. Takotsubo Cardiomyopathy: A Brief Review. *J. Med. Life* **2020**, *13*, 3–7. [CrossRef] [PubMed]
12. Boyd, B.M.; Solh, T.M. Takotsubo cardiomyopathy: Review of broken heart syndrome. *J. Am. Acad. Physician Assist.* **2020**, *33*, 24–29. [CrossRef] [PubMed]
13. Matta, A.G.; Carrié, D. Epidemiology, Pathophysiology, Diagnosis, and Principles of Management of Takotsubo Cardiomyopathy: A Review. *Experiment* **2023**, *29*, e939020. [CrossRef] [PubMed]
14. de Chazal, H.M.; Del Buono, M.G.; Keyser-Marcus, L.; Ma, L.; Moeller, F.G.; Berrocal, D.; Abbate, A. Stress Cardiomyopathy Diagnosis and Treatment: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2018**, *72*, 1955–1971. [CrossRef]

15. Dias, A.; Gil, I.J.N.; Santoro, F.; Madias, J.E.; Pelliccia, F.; Brunetti, N.D.; Salmoirago-Blotcher, E.; Sharkey, S.W.; Eitel, I.; Akashi, Y.J.; et al. Takotsubo syndrome: State-of-the-art review by an expert panel—Part 1. *Cardiovasc. Revascularization Med.* **2019**, *20*, 70–79. [CrossRef]
16. Dias, A.; Gil, I.J.N.; Santoro, F.; Madias, J.E.; Pelliccia, F.; Brunetti, N.D.; Salmoirago-Blotcher, E.; Sharkey, S.W.; Eitel, I.; Akashi, Y.J.; et al. Takotsubo syndrome: State-of-the-art review by an expert panel—Part 2. *Cardiovasc. Revascularization Med.* **2019**, *20*, 153–166. [CrossRef]
17. Wittstein, I.S.; Thiemann, D.R.; Lima, J.A.C.; Baughman, K.L.; Schulman, S.P.; Gerstenblith, G.; Wu, K.C.; Rade, J.J.; Bivalacqua, T.J.; Champion, H.C. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N. Engl. J. Med.* **2005**, *352*, 539–548. [CrossRef]
18. Akashi, Y.J.; Goldstein, D.S.; Barbaro, G.; Ueyama, T. Takotsubo cardiomyopathy: A new form of acute, reversible heart failure. *Circulation* **2008**, *118*, 2754–2762. [CrossRef]
19. Miyazaki, S.; Kamiishi, T.; Hosokawa, N.; Komura, M.; Konagai, H.; Sagai, H.; Takamoto, T. Reversible left ventricular dysfunction "takotsubo" cardiomyopathy associated with hyperthyroidism. *Jpn. Heart J.* **2004**, *45*, 889–894. [CrossRef]
20. Ruiz, S.; Martinez-Marin, M.; Luque, P.; Nassar, N.; Oros, D. Takotsubo cardiomyopathy after cesarean section: A case report and literature review. *J. Obstet. Gynaecol. Res.* **2017**, *43*, 392–396. [CrossRef]
21. Citro, R.; Giudice, R.; Mirra, M.; Petta, R.; Baldi, C.; Bossone, E.; Piscione, F. Is Tako-tsubo syndrome in the postpartum period a clinical entity different from peripartum cardiomyopathy? *J. Cardiovasc. Med.* **2013**, *14*, 568–575. [CrossRef] [PubMed]
22. Titus, A.; Sattar, Y.; Patel, N.; Taha, A.; Sandhyavenu, H.; Gonuguntla, K.; Thyagaturu, H.; Almas, T.; Balla, S. In-Hospital Outcomes of Takotsubo Cardiomyopathy During the COVID-19 Pandemic: Propensity Matched National Cohort. *Curr. Probl. Cardiol.* **2023**, *48*, 101598. [CrossRef] [PubMed]
23. Manabe, O.; Naya, M.; Oyama-Manabe, N.; Koyanagawa, K.; Tamaki, N. The role of multimodality imaging in takotsubo cardiomyopathy. *J. Nucl. Cardiol.* **2019**, *26*, 1602–1616. [CrossRef] [PubMed]
24. Wittstein, I.S. The Sympathetic Nervous System in the Pathogenesis of Takotsubo Syndrome. *Heart Fail. Clin.* **2016**, *12*, 485–498. [CrossRef] [PubMed]
25. Anderson, J.L.; Horne, B.D.; Le, V.T.; Bair, T.L.; Min, D.B.; Minder, C.M.; Dhar, R.; Mason, S.; Muhlestein, J.B.; Knowlton, K.U. Spectrum of radionuclide perfusion study abnormalities in takotsubo cardiomyopathy. *J. Nucl. Cardiol.* **2022**, *29*, 1034–1046. [CrossRef]
26. Moscatelli, S.; Montecucco, F.; Carbone, F.; Valbusa, A.; Massobrio, L.; Porto, I.; Brunelli, C.; Rosa, G.M. An Emerging Cardiovascular Disease: Takotsubo Syndrome. *BioMed Res. Int.* **2019**, *2019*, 6571045. [CrossRef]
27. Pelliccia, F.; Kaski, J.C.; Crea, F.; Camici, P.G. Pathophysiology of Takotsubo Syndrome. *Circulation* **2017**, *135*, 2426–2441. [CrossRef]
28. Galiuto, L.; De Caterina, A.R.; Porfidia, A.; Paraggio, L.; Barchetta, S.; Locorotondo, G.; Rebuzzi, A.G.; Crea, F. Reversible coronary microvascular dysfunction: A common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome. *Eur. Heart J.* **2010**, *31*, 1319–1327. [CrossRef]
29. Patel, S.M.; Lerman, A.; Lennon, R.J.; Prasad, A. Impaired coronary microvascular reactivity in women with apical ballooning syndrome (Takotsubo/stress cardiomyopathy). *Eur. Heart J. Acute Cardiovasc. Care* **2013**, *2*, 147–152. [CrossRef]
30. Buchmann, S.J.; Lehmann, D.; Stevens, C.E. Takotsubo Cardiomyopathy—Acute Cardiac Dysfunction Associated With Neurological and Psychiatric Disorders. *Front. Neurol.* **2019**, *10*, 917. [CrossRef]
31. Mejía-Rentería, H.D.; Núñez-Gil, I.J. Takotsubo syndrome: Advances in the understanding and management of an enigmatic stress cardiomyopathy. *World J. Cardiol.* **2016**, *8*, 413–424. [CrossRef] [PubMed]
32. Namgung, J. Electrocardiographic Findings in Takotsubo Cardiomyopathy: ECG Evolution and Its Difference from the ECG of Acute Coronary Syndrome. *Clin. Med. Insights Cardiol.* **2014**, *8*, 29–34. [CrossRef] [PubMed]
33. Priya, S.; Nagpal, P.; Aggarwal, T.; Huynh, J.; Khandelwal, K.; Khandelwal, A. Review of multi-modality imaging update and diagnostic work up of Takotsubo cardiomyopathy. *Clin. Imaging* **2021**, *80*, 334–347. [CrossRef] [PubMed]
34. Ahmed, K.A.; Madhavan, M.; Prasad, A. Brain natriuretic peptide in apical ballooning syndrome (Takotsubo/stress cardiomyopathy): Comparison with acute myocardial infarction. *Coron. Artery Dis.* **2012**, *23*, 259–264. [CrossRef] [PubMed]
35. Gopalakrishnan, P.; Zaidi, R.; Sardar, M.R. Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis. *World J. Cardiol.* **2017**, *9*, 723–730. [CrossRef] [PubMed]
36. Budnik, M.; Kochanowski, J.; Piatkowski, R.; Wojtera, K.; Peller, M.; Gaska, M.; Glowacka, P.; Karolczak, P.; Ochijewicz, D.; Opolski, G. Simple markers can distinguish Takotsubo cardiomyopathy from ST segment elevation myocardial infarction. *Int. J. Cardiol.* **2016**, *219*, 417–420. [CrossRef]
37. Sharkey, S.W.; Windenburg, D.C.; Lesser, J.R.; Maron, M.S.; Hauser, R.G.; Lesser, J.N.; Haas, T.S.; Hodges, J.S.; Maron, B.J. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J. Am. Coll. Cardiol.* **2010**, *55*, 333–341. [CrossRef]
38. Abe, Y.; Kondo, M.; Matsuoka, R.; Araki, M.; Dohyama, K.; Tanio, H. Assessment of clinical features in transient left ventricular apical ballooning. *J. Am. Coll. Cardiol.* **2003**, *41*, 737–742. [CrossRef]
39. Kawai, S.; Kitabatake, A.; Tomoike, H. Takotsubo cardiomyopathy study group guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. *Circ. J.* **2007**, *71*, 990–992. [CrossRef]
40. Bybee, K.A.; Prasad, A. Stress-related cardiomyopathy syndromes. *Circulation* **2008**, *118*, 397–409. [CrossRef]

41. de Souza, F.; Gismondi, R.A.O.C.; Neto, S.H.C.; de Mattos, M.A. Tako-tsubo-like cardiomyopathy and extra-adrenal pheochromocytoma: Case report and literature review. *Clin. Res. Cardiol.* **2008**, *97*, 397–401. [CrossRef] [PubMed]
42. Kato, K.; Kitahara, H.; Fujimoto, Y.; Sakai, Y.; Ishibashi, I.; Himi, T.; Kobayashi, Y. Prevalence and Clinical Features of Focal Takotsubo Cardiomyopathy. *Circ. J.* **2016**, *80*, 1824–1829. [CrossRef] [PubMed]
43. Ghadri, J.R.; Cammann, V.L.; Jurisic, S.; Seifert, B.; Napp, L.C.; Diekmann, J.; Bataiosu, D.R.; D'Ascenzo, F.; Ding, K.J.; Sarcon, A.; et al. A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: Results from the International Takotsubo Registry. *Eur. J. Heart Fail.* **2017**, *19*, 1036–1042. [CrossRef] [PubMed]
44. Citro, R.; Lyon, A.R.; Meimoun, P.; Omerovic, E.; Redfors, B.; Buck, T.; Lerakis, S.; Parodi, G.; Silverio, A.; Eitel, I.; et al. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: Clinical and prognostic implications. *J. Am. Soc. Echocardiogr.* **2015**, *28*, 57–74. [CrossRef] [PubMed]
45. Citro, R.; Okura, H.; Ghadri, J.R.; Izumi, C.; Meimoun, P.; Izumo, M.; Dawson, D.; Kaji, S.; Eitel, I.; Kagiyama, N.; et al. Multimodality imaging in takotsubo syndrome: A joint consensus document of the European Association of Cardiovascular Imaging (EACVI) and the Japanese Society of Echocardiography (JSE). *J. Echocardiogr.* **2020**, *18*, 199–224. [CrossRef] [PubMed]
46. Izumo, M.; Nalawadi, S.; Shiota, M.; Das, J.; Dohad, S.; Kuwahara, E.; Fukuoka, Y.; Siegel, R.J.; Shiota, T.; Lai, D.T.; et al. Mechanisms of acute mitral regurgitation in patients with takotsubo cardiomyopathy: An echocardio-graphic study. *Circ. Cardiovasc. Imaging* **2011**, *4*, 392–398. [CrossRef] [PubMed]
47. Bossone, E.; Lyon, A.; Citro, R.; Athanasiadis, A.; Meimoun, P.; Parodi, G.; Cimarelli, S.; Omerovic, E.; Ferrara, F.; Limongelli, G.; et al. Takotsubo cardiomyopathy: An integrated multi-imaging approach. *Eur. Heart J. Cardiovasc. Imaging* **2014**, *15*, 366–377. [CrossRef]
48. Lüscher, T.F.; Templin, C. Is takotsubo syndrome a microvascular acute coronary syndrome? Towards of a new definition. *Eur. Heart J.* **2016**, *37*, 2816–2820. [CrossRef]
49. Hirose, K.; Moriya, M.; Ishiwata, S.; Ohno, M. A case of Takotsubo cardiomyopathy that was confirmed by cardiac catheterization at all three times of onset. *J. Cardiol. Cases* **2015**, *12*, 152–155. [CrossRef]
50. Ghadri, J.-R.; Wittstein, I.S.; Prasad, A.; Sharkey, S.; Dote, K.; Akashi, Y.J.; Cammann, V.L.; Crea, F.; Galiuto, L.; Desmet, W.; et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur. Heart J.* **2018**, *39*, 2047–2062. [CrossRef]
51. Nayar, J.; John, K.; Philip, A.; George, L.; George, A.; Lal, A.; Mishra, A. A Review of Nuclear Imaging in Takotsubo Cardiomyopathy. *Life* **2022**, *12*, 1476. [CrossRef]
52. Sato, H.T.H.; Uchida, T. Takotsubo type cardiomyopathy due to multivessel spasm. In *Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure*; Kodama, K., Haze, K., Hon, M., Eds.; Kagakuhyouronsya Co.: Tokyo, Japan, 1990; pp. 56–64. (In Japanese)
53. Sato, H. Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In *Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure*; Kagakuhyoronsha Publishing Co.: Tokyo, Japan, 1990.
54. Brandspiegel, H.Z.; Marinchak, R.A.; Rials, S.J.; Kowey, P.R. A broken heart. *Circulation* **1998**, *98*, 1349. [CrossRef] [PubMed]
55. Matta, A.; Delmas, C.; Campelo-Parada, F.; Lhermusier, T.; Bouisset, F.; Elbaz, M.; Nader, V.; Blanco, S.; Roncalli, J.; Carrié, D. Takotsubo cardiomyopathy. *Rev. Cardiovasc. Med.* **2022**, *23*, 38. [CrossRef] [PubMed]
56. Sharkey, S.W.; Lesser, J.R.; Maron, M.S.; Maron, B.J. Why not just call it tako-tsubo cardiomyopathy: A discussion of nomenclature. *J. Am. Coll. Cardiol.* **2011**, *57*, 1496–1497. [CrossRef] [PubMed]
57. Eitel, I.; von Knobelsdorff-Brenkenhoff, F.; Bernhardt, P.; Carbone, I.; Muellerleile, K.; Aldrovandi, A.; Francone, M.; Desch, S.; Gutberlet, M.; Strohm, O.; et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* **2011**, *306*, 277–286. [CrossRef]
58. Di Filippo, C.; Bacchi, B.; Di Mario, C. Novel Aspects of Classification, Prognosis and Therapy in Takotsubo Syndrome. *Eur. Cardiol. Rev.* **2019**, *14*, 191–196. [CrossRef]
59. Gupta, S.; Gupta, M.M. Takotsubo syndrome. *Indian Heart J.* **2018**, *70*, 165–174. [CrossRef]
60. Matta, A.; Roncalli, J.; Elbaz, M.; Lhermusier, T.; Campelo-Parada, F.; Bouisset, F.; Elenizi, K.; Nader, V.; Carrié, D. Mid-Ventricular Takotsubo Cardiomyopathy with Hawk's Beak Appearance: A Case Report. *Am. J. Case Rep.* **2020**, *21*, e919563. [CrossRef]
61. Roncalli, J.; Carrie, D.; Fauvel, J.-M.; Losordo, D.W. A "hawk's beak" to identify the new transient midventricular Tako-Tsubo syndrome. *Int. J. Cardiol.* **2008**, *127*, e179–e180. [CrossRef]
62. Ennezat, P.V.; Pesenti-Rossi, D.; Aubert, J.M.; Rachenne, V.; Bauchart, J.J.; Auffray, J.L.; Logeart, D.; Cohen-Solal, A.; Asseman, P. Transient left ventricular basal dysfunction without coronary stenosis in acute cerebral disorders: A novel heart syndrome (inverted takotsubo). *Echocardiography* **2005**, *22*, 599–602. [CrossRef]
63. Sumida, H.; Morihisa, K.; Katahira, K.; Sugiyama, S.; Kishi, T.; Oshima, S. Isolated Right Ventricular Stress (Takotsubo) Cardiomyopathy. *Intern. Med.* **2017**, *56*, 2159–2164. [CrossRef] [PubMed]
64. Elesber, A.A.; Prasad, A.; Bybee, K.A.; Valeti, U.; Motiei, A.; Lerman, A.; Chandrasekaran, K.; Rihal, C.S. Transient cardiac apical ballooning syndrome: Prevalence and clinical implications of right ventricular involvement. *J. Am. Coll. Cardiol.* **2006**, *47*, 1082–1083. [CrossRef] [PubMed]
65. Van de Walle, S.O.; Gevaert, S.A.; Gheeraert, P.J.; De Pauw, M.; Gillebert, T.C. Transient stress-induced cardiomyopathy with an "inverted takotsubo" contractile pattern. *Mayo Clin. Proc.* **2006**, *81*, 1499–1502. [CrossRef] [PubMed]

66. Yasu, T.; Tone, K.; Kubo, N.; Saito, M. Transient mid-ventricular ballooning cardiomyopathy: A new entity of Takotsubo cardiomyopathy. *Int. J. Cardiol.* **2006**, *110*, 100–101. [CrossRef]
67. Aubert, J.M.; Ennezat, P.V.; Tricot, O.; Darchis, J.; Bauchart, J.J.; Auffray, J.L.; Lesenne, M.; Van Belle, E.; Goldstein, P.; Asseman, P. Mid-ventricular ballooning heart syndrome. *Echocardiography* **2007**, *24*, 329–334. [CrossRef]
68. Tamura, A.; Kawano, Y.; Watanabe, T.; Aso, T.; Abe, Y.; Yano, S.; Kadota, J. A report of 2 cases of transient mid-ventricular ballooning. *Int. J. Cardiol.* **2007**, *122*, e10–e12. [CrossRef]
69. Sanchez-Recalde, A.; Iborra, C.; Costero, O.; Moreno, R.; de Sá, E.L.; Sobrino, J.A.; López-Sendón, J.L. Isolated left ventricular basal ballooning in young women: "Inverted Takotsubo" pattern related to catecholamine-toxicity. *Am. J. Cardiol.* **2007**, *100*, 1496–1497. [CrossRef]
70. Kurowski, V.; Kaiser, A.; von Hof, K.; Killermann, D.P.; Mayer, B.; Hartmann, F.; Schunkert, H.; Radke, P.W. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy) frequency, mechanisms, and prognosis. *Chest* **2007**, *132*, 809–816. [CrossRef]
71. Cimarelli, S.; Sauer, F.; Morel, O.; Ohlmann, P.; Constantinesco, A.; Imperiale, A. Transient left ventricular dysfunction syndrome: Patho-physiological bases through nuclear medicine imaging. *Int. J. Cardiol.* **2010**, *144*, 212–218. [CrossRef]
72. Cimarelli, S.; Imperiale, A.; Ben-Sellem, D.; Rischner, J.; Detour, J.; Morel, O.; Ohlmann, P.; Constantinesco, A. Nuclear medicine imaging of takotsubo cardiomyopathy: Typical form and midventricular ballooning syndrome. *J. Nucl. Cardiol.* **2008**, *15*, 137–141. [CrossRef]
73. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med.* **2009**, *6*, e1000100. [CrossRef] [PubMed]
74. Singh, J. Critical appraisal skills programme. *J. Pharmacol. Pharmacother.* **2013**, *4*, 76–77. [CrossRef]
75. Miyajima, K.; Tawarahara, K.; Saito, N. Serial changes of myocardial perfusion imaging in takotsubo and reverse takotsubo cardiomyopathy. *J. Nucl. Cardiol.* **2022**, *29*, 2599–2611. [CrossRef] [PubMed]
76. Cadeddu, C.; Nocco, S.; Cadeddu, F.; Deidda, M.; Bassareo, P.; Serra, A.; Piga, M.; Mercuro, G. Inverted takotsubo cardiomyopathy induced by dobutamine stress echocardiography with atypical presentation. *Case Rep. Cardiol.* **2011**, *2011*, 413645. [CrossRef] [PubMed]
77. Moriya, M.; Naito, K.; Takahashi, M.; Ozoe, A.; Manabe, T.; Hosaka, H.; Suzuki, M. A case of transient mid-ventricular akinesia (a variant form of Takotsubo cardiomyopathy) followed with I-123-beta-metyl-iodophenyl pentadecanoic acid and I-123-meta-iodobenzyl-guanidine myocardial scintigraphy. *J. Cardiol.* **2009**, *53*, 140–145. [CrossRef] [PubMed]
78. Yoshikawa, M.; Yamamoto, T.; Shirakabe, A.; Ohno, T.; Tanaka, K. Myocardial scintigraphy in a patient with transient mid-ventricular ballooning cardiomyopathy: Case report. *Int. J. Cardiol.* **2007**, *119*, e8–e10. [CrossRef] [PubMed]
79. Yoshida, T.; Hibino, T.; Fujimaki, T.; Oguri, M.; Kato, K.; Yajima, K.; Ohte, N.; Yokoi, K.; Kimura, G. Transient mid-ventricular ballooning syndrome complicated by syncope: A variant of tako-tsubo cardiomyopathy. *Int. J. Cardiol.* **2009**, *135*, e20–e23. [CrossRef]
80. Nagai, T.; Konishi, T.; Arakawa, J.; Hisadome, H.; Tabata, H. Synchronicity of echocardiography and cardiac nuclear medicine in mid-ventricular ballooning syndrome: Paired 'ring signs' on polar maps. *Eur. Heart J. Cardiovasc. Imaging* **2014**, *15*, 947. [CrossRef]
81. Arao, K.; Ako, J.; Momomura, S.-I. Transient mid-ventricular ballooning: Insights from 123I-metaiodobenzylguanidine (MIBG) scintigraphy. *Int. J. Cardiol.* **2013**, *164*, e15–e16. [CrossRef]
82. Humbert, O.; Stamboul, K.; Gudjoncik, A.; Kanoun, S.; Richard, C.; Cochet, A.; Cottin, Y. Dual Diagnostic Role of 123I-MIBG Scintigraphy in Inverted-Takotsubo Pattern Cardiomyopathy. *Clin. Nucl. Med.* **2015**, *40*, 816–818. [CrossRef]
83. Ceccacci, A.; Mancone, M.; Calcagno, S.; De Vincentis, G.; Sardella, G.; Fedele, F. Role of MIBG scintigraphy in reverse Tako-tsubo cardiomyopathy: Confirming a pathophysiologic hypothesis. *Int. J. Cardiol.* **2016**, *223*, 54–55. [CrossRef] [PubMed]
84. Davis, M.; Hardebeck, C. Reverse Takotsubo syndrome diagnosed with Tc-99m SPECT perfusion study. *J. Nucl. Cardiol.* **2009**, *16*, 999–1002. [CrossRef] [PubMed]
85. Suzuki, K.; Osada, N.; Akasi, Y.J.; Suzuki, N.; Sakakibara, M.; Miyake, F.; Maki, F.; Takahashi, Y. An atypical case of "takotsubo cardiomyopathy" during alcohol withdrawal: Abnormality in the transient left ventricular wall motion and a remarkable elevation in the ST segment. *Intern. Med.* **2004**, *43*, 300–305. [CrossRef] [PubMed]
86. Ito, K.; Sugihara, H.; Kawasaki, T.; Yuba, T.; Doue, T.; Tanabe, T.; Adachi, Y.; Katoh, S.; Azuma, A.; Nakagawa, M. Assessment of ampulla (Takotsubo) cardiomyopathy with coronary angiography, two-dimensional echocardiography and 99mTc-tetrofosmin myocardial single photon emission computed tomography. *Ann. Nucl. Med.* **2001**, *15*, 351–355. [CrossRef] [PubMed]
87. Ito, K.; Sugihara, H.; Katoh, S.; Azuma, A.; Nakagawa, M. Assessment of Takotsubo (ampulla) cardiomyopathy using 99mTc-tetrofosmin myocardial SPECT—Comparison with acute coronary syndrom. *Ann. Nucl. Med.* **2003**, *17*, 115–122. [CrossRef] [PubMed]
88. Bybee, K.A.; Murphy, J.; Prasad, A.; Wright, R.S.; Lerman, A.; Rihal, C.S.; Chareonthaitawee, P. Acute impairment of regional myocardial glucose uptake in the apical ballooning (takotsubo) syndrome. *J. Nucl. Cardiol.* **2006**, *13*, 244–250. [CrossRef] [PubMed]
89. Fro, K.; Sugihara, H.; Kinoshita, N.; Azuma, A.; Matsubara, H. Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using99mTc-tetrofosmin,123I-BMIPP,123I-MIBG and99mTc-PYP myocardial SPECT. *Ann. Nucl. Med.* **2005**, *19*, 435–445. [CrossRef]

90. Obunai, K.; Misra, D.; Vantosh, A.; Bergmann, S.R. Metabolic evidence of myocardial stunning in takotsubo cardiomyopathy: A positron emission tomography study. *J. Nucl. Cardiol.* **2005**, *12*, 742–744. [CrossRef]
91. Perrone-Filardi, P.; Bacharach, S.L.; Dilsizian, V.; Marin-Neto, J.; Maurea, S.; Arrighi, J.A.; Bonow, R.O. Clinical significance of reduced regional myocardial glucose uptake in regions with normal blood flow in patients with chronic coronary artery disease. *J. Am. Coll. Cardiol.* **1994**, *23*, 608–616. [CrossRef]
92. Ueyama, T.; Hano, T.; Kasamatsu, K.; Yamamoto, K.; Tsuruo, Y.; Nishio, I. Estrogen attenuates the emotional stress-induced cardiac responses in the animal model of tako-tsubo (ampulla) cardiomyopathy. *J. Cardiovasc. Pharmacol.* **2003**, *42*, S117–S120. [CrossRef]
93. Paur, H.; Wright, P.T.; Sikkel, M.B.; Tranter, M.H.; Mansfield, C.; O'Gara, P.; Stuckey, D.J.; Nikolaev, V.O.; Diakonov, I.; Pannell, L.; et al. High levels of circulating epinephrine trigger apical cardiodepression in a β2 -adrenergic receptor/Gi –dependent manner: A new model of Takotsubo cardiomyopathy. *Circulation* **2012**, *126*, 697–706. [CrossRef] [PubMed]
94. Lyon, A.R.; Rees, P.S.C.; Prasad, S.; Poole-Wilson, P.A.; Harding, S.E. Stress (Takotsubo) cardiomyopathy—A novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat. Clin. Pract. Cardiovasc. Med.* **2008**, *5*, 22–29. [CrossRef] [PubMed]
95. Mori, H.; Ishikawa, S.; Kojima, S.; Hayashi, J.; Watanabe, Y.; I E Hoffman, J.; Okino, H. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. *Cardiovasc. Res.* **1993**, *27*, 192–198. [CrossRef] [PubMed]
96. Kawano, H.; Okada, R.; Yano, K. Histological study on the distribution of autonomic nerves in the human heart. *Heart Vessel.* **2003**, *18*, 32–39. [CrossRef] [PubMed]
97. Ghadri, J.R.; Jaguszewski, M.; Corti, R.; Lüscher, T.F.; Templin, C. Different wall motion patterns of three consecutive episodes of takotsubo cardiomyopathy in the same patient. *Int. J. Cardiol.* **2012**, *160*, e25–e27. [CrossRef] [PubMed]
98. Akashi, Y.J.; Nakazawa, K.; Sakakibara, M.; Miyake, F.; Musha, H.; Sasaka, K. 123I-MIBG myocardial scintigraphy in patients with 'takotsubo' cardiomyopathy. *J. Nucl. Med.* **2004**, *45*, 1121–1127. [PubMed]
99. Burgdorf, C.; von Hof, K.; Schunkert, H.; Kurowski, V. Regional alterations in myocardial sympathetic innervation in patients with transient left-ventricular apical ballooning (Tako-Tsubo cardiomyopathy). *J. Nucl. Cardiol.* **2008**, *15*, 65–72. [CrossRef]
100. Pontico, M.; Brunotti, G.; Conte, M.; Corica, F.; Cosma, L.; De Angelis, C.; De Feo, M.S.; Lazri, J.; Matto, A.; Montebello, M.; et al. The prognostic value of 123I-mIBG SPECT cardiac imaging in heart failure patients: A systematic review. *J. Nucl. Cardiol.* **2022**, *29*, 1799–1809. [CrossRef]
101. Verschure, D.; Poel, E.; De Vincentis, G.; Frantellizzi, V.; Nakajima, K.; Gheysens, O.; de Groot, J.R.; Verberne, H.J. The relation between cardiac 123I-*m*IBG scintigraphy and functional response 1 year after CRT implantation. *Eur. Heart J. Cardiovasc. Imaging* **2021**, *22*, 49–57. [CrossRef]
102. De Vincentis, G.; Frantellizzi, V.; Fedele, F.; Farcomeni, A.; Scarparo, P.; Salvi, N.; Fegatelli, D.A.; Mancone, M.; Verschure, D.O.; Verberne, H.J. Role of cardiac 123I-mIBG imaging in predicting arrhythmic events in stable chronic heart failure patients with an ICD. *J. Nucl. Cardiol.* **2019**, *26*, 1188–1196. [CrossRef]
103. Knuuti, J.; Sipola, P. Is it time for cardiac innervation imaging? *Q. J. Nucl. Med. Mol. Imaging* **2005**, *49*, 97–105. [PubMed]
104. De Vincentis, G.; Frantellizzi, V. The 123I-mIBG heart/mediastinum ratio: Moving from 2D to 3D imaging. *J. Nucl. Cardiol.* **2021**, *28*, 2578–2580. [CrossRef] [PubMed]
105. Deibert, D.C.; Defronzo, R.A. Epinephrine-induced insulin resistance in man. *J. Clin. Investig.* **1980**, *65*, 717–721. [CrossRef] [PubMed]
106. Shepherd, P.R.; Kahn, B.B. Glucose transporters and insulin action—Implications for insulin resistance and diabetes mellitus. *N. Engl. J. Med.* **1999**, *341*, 248–257. [CrossRef] [PubMed]
107. A Cohen, R.; Shepherd, J.T.; Vanhoutte, P.M. Prejunctional and postjunctional actions of endogenous norepinephrine at the sympathetic neuroeffector junction in canine coronary arteries. *Circ. Res.* **1983**, *52*, 16–25. [CrossRef] [PubMed]
108. Meimoun, P.; Malaquin, D.; Sayah, S.; Benali, T.; Luycx-Bore, A.; Levy, F.; Zemir, H.; Tribouilloy, C. The coronary flow reserve is transiently impaired in tako-tsubo cardiomyopathy: A prospective study using serial doppler transthoracic echocardiography. *J. Am. Soc. Echocardiogr.* **2008**, *21*, 72–77. [CrossRef] [PubMed]
109. Vitale, C.; MC Rosano, G.; Kaski, J.C. Role of Coronary Microvascular Dysfunction in Takotsubo Cardiomyopathy. *Circ. J.* **2016**, *80*, 299–305. [CrossRef]
110. Elesber, A.; Lerman, A.; Bybee, K.A.; Murphy, J.G.; Barsness, G.; Singh, M.; Rihal, C.S.; Prasad, A. Myocardial perfusion in apical ballooning syndrome: Correlate of myocardial injury. *Am. Heart J.* **2006**, *152*, 469.e9–469.e13. [CrossRef]
111. Kume, T.; Akasaka, T.; Kawamoto, T.; Yoshitani, H.; Watanabe, N.; Neishi, Y.; Wada, N.; Yoshida, K. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. *Circ. J.* **2005**, *69*, 934–939. [CrossRef]