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Plasma Epinephrine Level and its Causal Link to Takotsubo Syndrome Revisited: Critical Review with a Diverse Conclusion

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ABSTRACT

Takotsubo syndrome (TS) is a recognized acute cardiac syndrome with a clinical presentation resembling that of an acute coronary syndrome (ACS). The defining feature of TS is the reversible left ventricular wall motion abnormality (LVWMA), which has a unique circumferential pattern resulting in a conspicuous ballooning of the left ventricle during systole, and extending beyond the coronary artery supply territory. The pathogenesis of TS is still elusive and several pathophysiological mechanisms have been proposed. A common portrayal of the syndrome in the literature is that the disease is characterized by massive surge of plasma catecholamines including epinephrine. Based on the assumption of massive plasma epinephrine elevation, some investigators hypothesized that the circulatory plasma epinephrine plays a pivotal role in the pathogenesis of TS. One typical such hypothesis is epinephrine induced switch in signal trafficking causing apical or mid-apical ballooning in TS. In-depth analysis of the literature reveals that no study with certainty has shown "massive" plasma epinephrine elevations in TS. Furthermore, the literature evidences challenging the epinephrine-induced switch in signal trafficking are substantial. In this review, sufficient data, indicating that the plasma epinephrine in TS is either normal or moderately elevated in all studies, are provided. Noteworthy, epinephrine may act as a trigger factor for TS-induction but there is no evidence for a direct causal link between epinephrine and TS.

Contents

1. Introduction

Takotsubo syndrome (TS) is a recognized acute cardiac syndrome with a clinical presentation resembling that of an acute coronary syndrome (ACS) [1,2]. The term takotsubo (tako = octopus, tsubo = a pot) was introduced by Sato and Dote in 1990 and 1991 to describe the left ventricular silhouette during systole in 5 patients presenting with clinical features of myocardial infarction but without obstructive coronary artery disease [3,4]. The defining feature of TS is the reversible left ventricular wall motion abnormality (LVWMA), which has a unique circumferential pattern resulting in a conspicuous ballooning of the left ventricle during systole, and extending beyond the coronary artery

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supply territory [1,5]. The LVWMA may be localized to the apical, mid-apical, mid-ventricular, mid-basal or basal segments of the left ventricle [1,5]. Focal and global left ventricular contractile abnormalities have also been reported [2,6]. The right ventricle is involved in about one third of patients with TS [7]. Cases of isolated right ventricular involvement in TS have also been reported [8]. The pathogenesis of TS is still elusive [2,9–11]. A well-known described feature of the syndrome in the literature is that the disease is characterized by massive elevation of plasma catecholamine including epinephrine [12]. Based on the supposition of massive plasma epinephrine elevation, some investigators hypothesized that epinephrine-induced switch in signal trafficking at the apical region of the left ventricle, causing apical or mid-apical ballooning in TS, is pivotal in the pathogenesis of TS [13]. In-depth analysis of the literature reveals in fact that no study with certainty has shown massive plasma epinephrine elevation in TS. The literature evidences challenging the epinephrine-induced switch in signal trafficking causing TS is substantial [1,10]. In this review, sufficient data indicating that the plasma epinephrine in TS is either normal or moderately elevated in all studies, are provided. Moreover, there is no evidence for a direct causal link between epinephrine and TS. However, epinephrine as any other physical stressor may act as a trigger factor for TS-induction [14]. Epinephrine-induced TS is associated with high complication rates as heart failure and cardiogenic shock [14] and it should be remembered that treatment with inotropic agents in such cases is contraindicated [5].

2. Back-ground to the report of massive plasma epinephrine elevation in takotsubo syndrome

It is often reported in the literature that TS is characterized by a massive surge of catecholamines including epinephrine despite normal or moderately elevated plasma epinephrine in most of the studies. A typical statement in the literature is: "Wittstein and colleagues demonstrated massively elevated catecholamines and stress-related neuropeptides compared with patients with Killip III myocardial infarction" [15]. This is based on a study published by Wittestein and colleagues in 2005, where plasma catecholamine (including epinephrine) and stress-related neuropeptide levels in 13 patients with TS triggered by emotional stressors were compared with 7 patients with Killip class III myocardial infarction [12]. The study showed "extremely high levels" of plasma catecholamines and stress related neuropeptides. The plasma catecholamine levels (including epinephrine) remained markedly elevated even a week after the onset of symptoms. In that report, the plasma epinephrine levels were 34.16 (day 1,2), 28.22 (day 3,4,5), and 9.41 (day 7,8,9) times the normal "published" values (Fig. 1). The corresponding levels for the plasma metanephrine were 3.02, 8.62, and 11.17 times the normal "published" values respectively (Fig. 1). Consequently, "extremely high levels" of both plasma epinephrine and metanephrine during the whole week after the onset of symptoms were reported. Similar plasma catecholamine levels have been reported in patients with pheochromocytoma-induced TS [16–18]. Relying on the supposition of massive epinephrine elevation, some investigators have suggested a direct causal link between epinephrine and TS [13]. The differences in plasma epinephrine levels between those measured by Wittstein and colleagues, and those measured in all other studies (Figs. 2, 3, and 4 and Table 1 discussed below) are so huge that a well thought-out and sustainable explanation needs to be provided.

3. Other literature data on plasma epinephrine levels in TS

The "massive surge of plasma epinephrine" in TS patients reported by Wittstein et al. [12] has not been reinforced in any other study (Figs 2, 3, 4 and Table 1). Kurisu et al., [19] in a study of 30 patients with TS, measured plasma catecholamines in 6 patients. They found normal average circulating epinephrines. Plasma epinephrine ranged in that study from 21 to 131 pg/mL (91 ± 54 pg/mL, normal <100 pg/mL). Twenty-four-hours urine measurement for epinephrine levels were normal in the 3 patients in whom this variable was measured in another study [20]. Yoshioka et al. [21] found no causal relationship between TS and the transient mild elevation of the catecholamines. In that study, the elevation of catecholamines was related to the severity of killip class. Kume et al. [22] reported on increased local release of norepinephrine from the heart in 5 consecutive patients with TS. Critical review of the measurements of the plasma levels of catecholamines in the same study showed normal plasma epinephrine levels in 3 patients, just above the normal reference value in one patient and moderate elevation in only one patient (135, 423, 53, 99, and 41 pg/mL, normal <100 pg/mL). Morel et al. [23] found normal average plasma epinephrine on day 1 of admission and at 10 months follow up in 8 patients with TS (324 ± 198 pM/L, normal <550 pM/L). In addition, there were no differences in the plasma level of epinephrine between

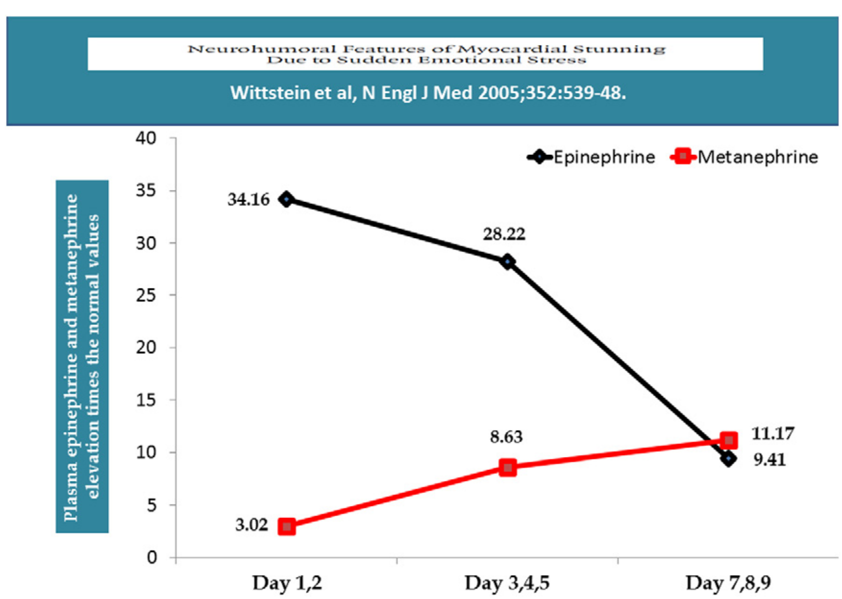

Fig. 1. Massive plasma epinephrine and metanephrine elevation times the published normal values (epinephrine 37 pg/mL, metanephrine 59 pg/mL, data from Goldstein et al. [30]) on three occasions during the first week of admission according to the results from Wittstein and colleagues [12].

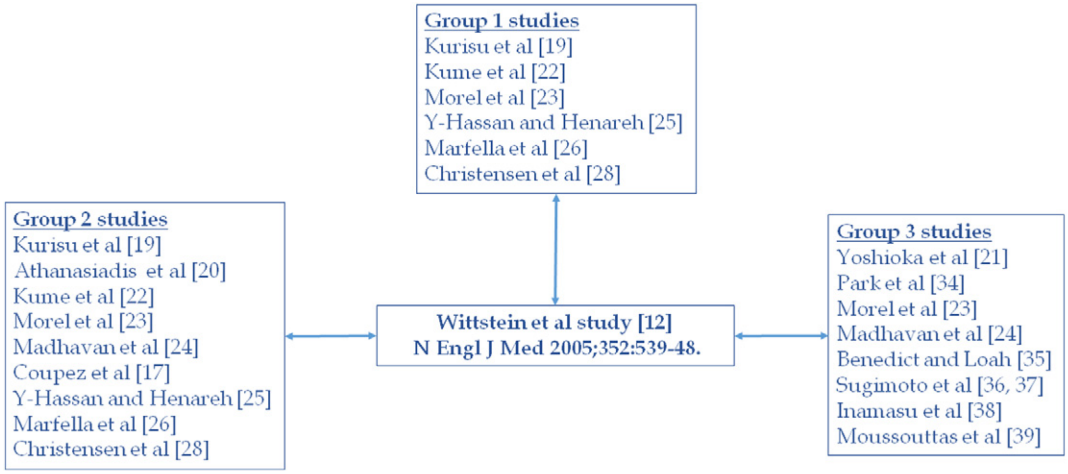

Fig. 2. The study groups compared to Wittstein study. In group 1 studies, the mean or median plasma epinephrine elevation times the upper normal limits could be calculated and compared to Wittstein study (see also Figs. 3 and 4). In group 2 studies, the urinary epinephrine, plasma metanephrine or urinary metanephrine if available in addition to plasma epinephrine compared with Wittstein study (See also Figs 1, 3, 4 and Table 1). Evidences supporting the fact that the plasma epinephrine is normal or moderately elevated in TS and no significant difference in plasma epinephrine elevation in TS compared to other acute medical illnesses are provided in group 3 studies.

the patients with TS and the control group, comprised of 14 age-matched patients hospitalized in the cardiology department during the same period (319 ± 156 pM/L). Madhavan et al. [24] reported on plasma levels of free fractionated metanephrines, including metanephrine and noremetanephrine in 19 patients with TS and 10 patients with ST-elevation myocardial infarction (STEMI). The plasma levels of fractionated metanephrine were normal in all patients in both groups. Twenty-four-hour urine levels of fractionated catecholamines and metanephrines were normal in all patients with TS. Coupez et al. [17] measured the urinary metanephrine and normetanephrine in 19 patients with TS within the first 3 consecutive days after admission. The mean total, the mean urinary metanephrine and the mean urinary normetanephrine concentration were normal in the emotionally and physically triggered TS while understandably markedly elevated in pheochromocytoma/paraganglioma induced TS. Y-Hassan and Henareh [25] measured plasma epinephrine during the first few days of admission in 27 patients with TS. Plasma epinephrine was normal in 24 of 27 patients (89%); was moderately elevated (3.8-fold the upper normal limit) in 2 patients and markedly elevated in only one patient (8.9-fold the upper normal limit). Marfella et al. [26] measured plasma epinephrine levels in 48 patients with TS at admission and 12 months follow up. The mean and the median plasma epinephrine levels during subacute stage were increased to 2.13-fold the upper normal limit. This has been confirmed in a reply to comment where the authors have stated "Marfella et al. reported the elevation of plasma catecholamines (two- to threefold of the normal values for epinephrine and less than twofold for norepinephrine)" [27]. The interquartile range for epinephrine in Marfella's study was 758–1240 pg/mL; this implies that about 25% of patients had epinephrine values <758 pg/mL, namely near normal or very slight

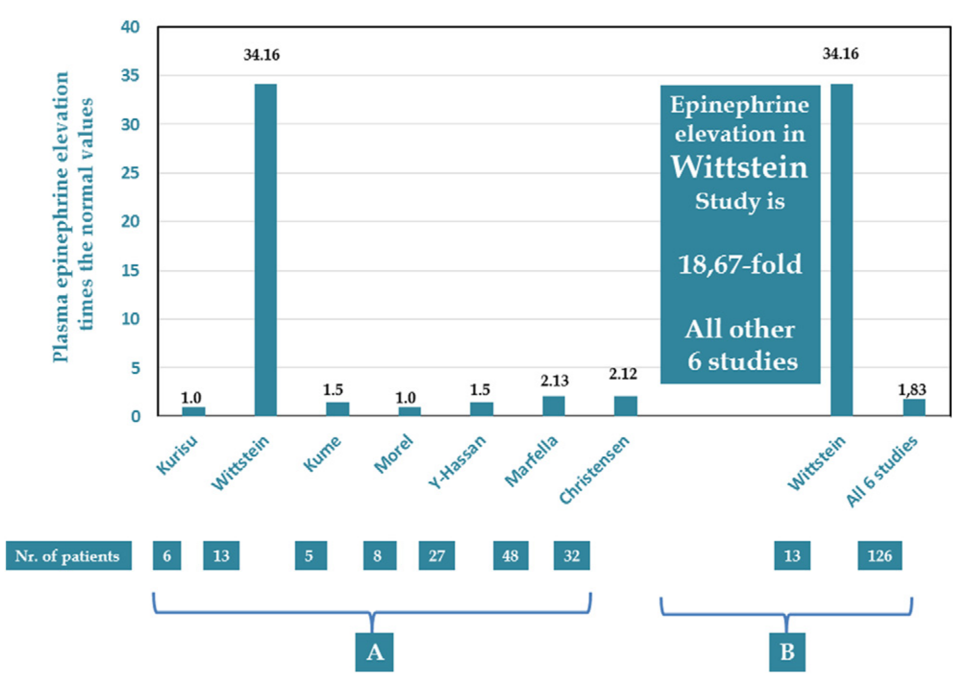

Fig. 3. The massive plasma epinephrine elevation times the normal published values reported by Wittstein and Colleagues compared to the normal, mild or moderate elevations in 6 other studies. The epinephrine elevation in Wittstein study stands out peculiarly compared to all other 6 studies (A). The discrepancy is huge that the massive elevation in the 13 patients in Wittstein study was 18.67 times the elevation in all other 6 studies (126 patients) taken together (B). The values seen in the figure is expressed as multiples of the upper limit of normal (ULN) if available or multiples of the mean normal value if ULN is not available.

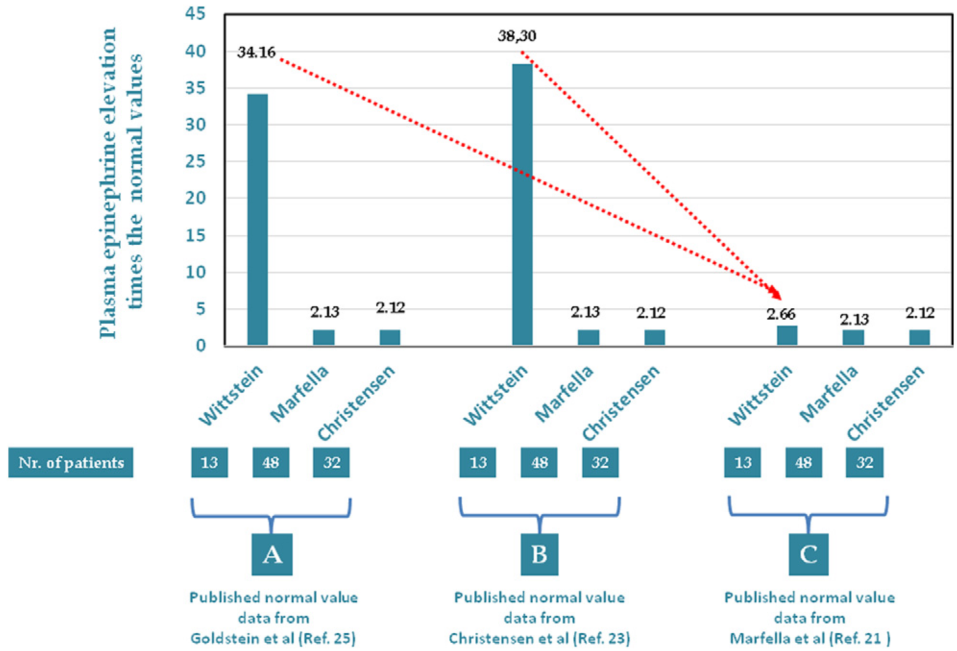

Fig. 4. The degree of plasma epinephrine elevations in Wittstein study depends on which published normal values are used. A, the immense difference between the plasma epinephrine elevation times the published normal values (if data from Goldstein et al. are used as the original study) in Wittstein study and the mild-moderate epinephrine elevation times the normal values in 2 other studies (Marfella et al. and Christensen et al.). B, even larger difference between plasma epinephrine elevations times the published value (if the normal values published in Christensen et al. is used) in Wittstein study and the mild-moderate elevations in the same other 2 studies. C, no difference in plasma epinephrine elevations times the normal values is noted between all the three studies (if the published normal value from Marfella et al. is used). The values seen in C are in fact the most appropriate calculations to be used, discussed in the main manuscript. The values are expressed as multiples of the ULN.

elevation of epinephrine. In another study comprising of 32 patients with TS, Christensen et al. [28] measured plasma epinephrine levels in the subacute stage of the disease (day 2–4) and found that mean plasma Log2 [epinephrine] levels were increased to 1.35-fold the normal mean (available) level. The median plasma epinephrine levels were increased to 2.12-fold the upper normal limit (normal value 17–33 pg/mL). Worth to mention that even in this study some patients had completely normal plasma epinephrine levels [29].

3.1. The reasons for the huge discrepancy between one study and many other studies

Fig. 3A illustrates the big differences in plasma epinephrine levels between Wittstein et al. [12] study and 6 other studies where the plasma epinephrine (mean or median) levels times the normal value could be calculated. Taken together, the patients in Wittstein et al. study had 18.67 times higher plasma epinephrine levels than patients

Table 1
The studies where plasma or urine epinephrine and/or metanephrine measured and compared to the study performed by Wittstein el al.

Study	Year	Nr. of patients epineph or metaneph measured/nr of patients in the whole study	Age (mean or median)	Gender F/M	TS ballooning pattern	Trigger factor (E/P)	P. Epinephrine or metanephrines levels
Kurisu et al. [19]	2002	6/30	70 ± 8	28F/2M	Apical (described as takotsubo-like)	10 (5E, 5P) of 30 had trigger factor	(91 ± 54 pg/mL) Normal
Wittstein et al. [12]	2005	13/19	63 (median age)	18F/1M	All apical ballooning pattern	All emotional	Massive elevations of both plasma epinephrine and metanephrines
Kume et al. [22]	2008	5/5	76 (median age)	3F/2M	Mid-apical ballooning	All physical	Normal in 4 and mild elevation in one
Morel et al. [23]	2009	8/17	72.5 ± 9	8F/0M	Apical ballooning	11 of 17 the whole study had preceding emotional stress	Normal
Madhavan et al. [24]	2009	19/19	70 (61–80)	18F/1M	Apical ballooning	5E/10P	Normal Plasma fractionated metanephrine in all 19 patients
Coupez et al. [17]	2014	19/40	65 ± 13	34F/6M	Apical ballooning	29E, 5P, 3Adrenergic intoxication, 3 pheochromocytoma	Normal urinary metanephrine in emotional and physical induced TS but not in pheochromocytoma
Y-Hassan and Henareh [25]	2015	27/33	65 ± 12	29F/4M	15 apical or mid-apical, 16 mid-ventricular, 2 basal or mid-basal	15E, 14P, 4 none	Plasma epinephrine and metanephrine were normal in 89% and 79% of patients respectively
Marfella et al. [26]	2016	48/48	63 ± 5.8	48F/0M	All mid-apical ballooning	N/A	Plasma epinephrine moderately elevated, 2.13-fold times the UNL
Christensen et al. [28]	2016	32/32	68 (63–73)	30F/2M	All apical ballooning	10E, 12P	Plasma epinephrine moderately elevated, 2.12 –fold times the UNL

E, emotional; Epineph, epinephrine; F, female; metaneph, metanephrine; M, male; N/A, not avilable; Nr, number; P, physical; TS, takotsubo syndrome; UNL, upper normal limit;

in all other 6 studies (Fig. 3B). Among the other 6 studies, Marfella et al. [26] and Christensen et al. [28]reported highest plasma epinephrine levels, which were 2.13 and 2.12 times the upper normal limits respectively. This implies that the plasma epinephrine levels in Wittstein study was 16,04 and 16.11 times higher than that measured by Marfella et al. [26] and Christensen et al. [28] studies respectively. This difference is so immense that a reasonable and sustainable explanation should be provided. The heterogeneity of stressors between studies, the timing of blood draw in relation to the initial trigger and the differences in technique between laboratories are among the reasons given for the inconsistent findings between the studies [15]. However, substantial numbers of TS patients in the studies which showed normal or moderate elevation of plasma epinephrine levels were also preceded by emotional stressors as that in the 13 patients reported by Wittstein and colleagues [17,24,25] (Table 1). If the plasma epinephrine levels were persistently elevated from day 1 to day 9 in Wittstein study, the timing of blood draw should not play any role on the values if the measurement is done within one week of admission in patients with TS. Such extreme high plasma catecholamine levels measured by Wittstein et al. should be reproduced by any technique used at any laboratory. Other more rational explanations should be sought after. One important statement found in the original paper published by Wittstein and Colleagues, which may explain the discrepancy between the studies is the following: "On hospital day 1 or 2, plasma levels of catecholamines (i.e., epinephrine, norepinephrine, and dopamine) among patients with stress cardiomyopathy were 2 to 3 times the values among patients with Killip class III myocardial infarction and *7 to 34 published normal values*". I believe that the use of *"the published normal values"* and not the normal values of the laboratory where plasma epinephrine was measured is the most plausible explanation for the obtained extremely high levels measured in Wittstein study. The 37 pg/mL normal published plasma epinephrine value, according to Table 2 in Wittstein study [12], is data from Goldstein et al. [30].

4. Recalculation of the plasma epinephrine in TS in Wittstein study according to published values

If recalculation of the plasma epinephrine elevation in Wittstein study is done, using the normal published values by either Marfella [26] or Christensen [28] instead of Goldstein data [30], the results will be spectacularly different. The median plasma epinephrine level in Wittstein study is 1264 pg/mL on day 1,2, a level which is comparable to that measured by Marfella study (1013 pg/mL) whereas it was 18 times higher than that measured by Christensen et al. (70 pg/mL). The normal reference value for plasma epinephrine in Marfella et al. study is <500 pg/mL (noted in 12 months follow up values and confirmed by the reply comment by Sardu et al. [27]). The normal reference limits for plasma epinephrine in Christensen et al. study was 17–33 pg/mL. When using, the normal published value by Christensen study, the plasma epinephrine elevation in Wittstein study will be even higher i.e. 38.30 times the normal published value by Christensen et al. (Fig. 4B). In contrast, there is no remarkable difference in the plasma epinephrine elevation between Wittstein and Marfella studies (1264 vs 1013 pg/mL, 1.25 times). Consequently, it will be much more sensible to use the normal published values in Marfella study (<500 pg/mL) to calculate the degree of epinephrine elevation in Wittestein study. In such a case the elevation of plasma epinephrine levels in Wittstein study will be 2.66 instead of 34.16 times the published values (Fig. 4C). This will give results, which are more reasonable and comparable to all other studies as clearly depicted in Fig. 4A, B, and C. Interestingly, when using the appropriate published normal value, the level of plasma epinephrine measured during day 7,8 and 9 in Wittstein study will be completely normal i.e. 0.70 times the normal published levels. Consequently, the main reason for the immense discrepancy between the "massive" elevation of plasma epinephrine in Wittstein study and the normal, mild or moderate elevation in all other studies in patients with TS is, regrettably to say, the use, in my opinion, of inaccurate normal published values. Plausibly, the most appropriate way to deem an elevation of a laboratory value is to compare it with the reference value in that laboratory. Thus, the plasma epinephrine levels are moderately elevated in Wittsein et al. study just like most of other studies. Another interesting finding in the 13 patients described in Wittstein study, challenging massive elevation of catecholamines including plasma epinephrine is the takotsubo localization pattern. One may expect apical sparing takotsubo pattern at least in some of the 13 patients. Almost 50% of patients with epinephrine- or pheochromocytoma-triggered TS have apical sparing pattern of TS, whereas all the 13 patients in Wittstein study had apical pattern of TS [14,16,31–33].

5. No difference in plasma epinephrine levels between patients with TS and other acute medical illnesses

Plasma epinephrine level is either normal or moderately elevated in patients with TS just like epinephrine elevations occurring in other acute medical diseases (Fig. 2). Park et al. [34] reported no significant difference in the level of plasma epinephrine (log value) in patients admitted to the intensive care unit with acute non-cardiac physical illnesses with (26 patients) or without (66 patients) left ventricular apical ballooning (2.4 ± 0.7 vs 2.2 ± 0.7, $p = 0.336$), whereas there was significant difference in the level of plasma norepinephrine (log value) between patients with and without left ventricular apical ballooning (3.2 ± 1.0 vs 2.5 ± 0.7, $p = 0.004$). Morel et al. [23] found no differences in plasma epinephrine levels in the 8 patients with TS (324 $\pm$ 198 pM/L, normal, <550 pM/L) and the control group, comprised of 14 age-matched patients hospitalized in the cardiology department during the same period (319 $\pm$ 156 pM/L). Madhavan et al. [24] reported no difference in plasma-free metanephrine (epinephrine metabolite) in 19 patients with TS and 10 control patients with STEMI. This fact has also been well-demonstrated in patients with subarachnoid hemorrhage (SAH), which is a recognized trigger factor for TS. Significant plasma norepinephrine elevations in patients SAH and TS has been reported, reflecting the role of sympathetic nervous system in the pathogenesis of TS [35–39], which is in line with the evidences for the involvement of the sympathetic nervous system including cardiac sympathetic nervous system in TS triggered by other emotional or physical stressors [5,40]. The plasma epinephrine concentrations in patients with SAH were not significantly greater than those of the patients in a subgroup with other pathology in a study by Benedict and Loach [35] measuring plasma adrenaline and noradrenaline in 21 patients with SAH and in 13 control patients. Plasma epinephrine levels were not correlated with SAH-induced LVWMA in a retrospective analysis on 77 patients with SAH (23 men, 54 women) whose plasma levels of epinephrine, norepinephrine and estradiol ES had been measured and echocardiogram had been obtained within 48 h of SAH onset in a study published by Sugimoto et al. [36]. In another study, Sugimoto et al. [37] reported on 48 patients with SAH who underwent both trans-thoracic echocardiography and measurement of plasma catecholamine levels within 24 h of SAH onset. There was no significant difference in the level of plasma epinephrine levels between patients with LVWMA and those without LVWMA. Inamasu et al. [38] reported on 63 patients with SAH (20 men and 43 women). Seven patients (11%) developed neurogenic pulmonary edema (NPE), where most of them (6 of 7, 86%) had LVWMA. There was no significant difference in plasma epinephrine levels between patients with NPE and those without NPE. By contrast, plasma norepinephrine levels were significantly higher in patients with NPE than those without NPE. Moussouttas et al. [39] reported elevation of plasma catecholamine levels in patients with SAH and TS-like LVWMA. The TS-like LVWMA was primarily related to elevated plasma norepinephrine levels. Plasma epinephrine was elevated but there were no differences between patients with or without LVWMA.

6. Epinephrine and pathophysiology of takotsubo syndrome

The findings of normal plasma epinephrine in a substantial number of patients with TS, and mild to moderate elevations in the remainder comparable to epinephrine elevations in association with other non-cardiac diseases argue against a direct causal link between plasma epinephrine levels and TS.

7. Epinephrine-induced switch in signal trafficking as a cause of TS

In 2008, Lyon et al. [13] hypothesized that high levels of circulating epinephrine trigger a switch in the intracellular signal trafficking from Gs (simulatory) protein to Gi (inhibitory) protein signaling through B2 adrenoreceptors (B2ARs). The authors suggested that this change in signaling is negatively inotropic and that the effect is greatest at the apical myocardium explaining the apical ballooning seen in TS (Fig. 5). In an animal model of TS, Paur et al. [41] reported that injection of high bolus dose epinephrine can trigger left ventricular apical ballooning. They suggested that biased agonism of epinephrine for the stimulatory G-protein-activated cardio-stimulant at low concentration and for inhibitory G-protein-activated cardio-depressant pathway at high concentration underpins the acute apical cardio-depression observed in TS (Fig. 5). The investigators have explained the differential regional responses of the left ventricle based on an apical-basal gradient in B2ARs. However, reports of recurrences of TS with variant forms (mid-ventricular pattern as a recurrence of typical apical pattern and vice versa) suggest rather a homogenous ventricular adrenoceptor density [42,43]. In addition, many other clinical findings in patients with TS challenge this suggested pathologic mechanism. Paur et al. have based their suggestion on the presumed fact that in patients with TS, there will be an extreme surge of epinephrine in response to the triggering stressor or coexisting medical condition. Such extreme high concentration of epinephrine has not been measured in any study including the one reported by Wittstein et al. [12] on painstaking analysis of the study. Several studies have reported normal plasma epinephrine and plasma or urine metanephrine in most patients with TS [17,24,25]. Plasma epinephrine and metanephrine were completely normal in 89% and 79% respectively in one study [25]. Paur et al. in their study have reported only apical ballooning during high bolus epinephrine injection. The epinephrine-induced apical ballooning could not be reproduced in another animal model. Redfors et al. [44] induced mainly basal type of TS during injection of epinephrine in rats. Kumai et al. [45] reported that in patient with TS triggered by subarachnoid hemorrhage, the plasma epinephrine was significantly higher in "revered TS" than those with apical TS, a finding, which argues against the apical epinephrine-induced switch in signal trafficking hypothesis. Furthermore, this hypothesis fails to explain the basal (inverted) and other apical sparing patterns of TS seen in some patients. Substantial numbers of clinical cases of TS triggered by therapeutic or accidental administration of epinephrine or triggered by pheochromocytoma are apical sparing types (mid-ventricular, mid-basal or basal types) [31,32]. One third of patients had basal (inverted) pattern and almost 50% of patients had apical sparing pattern in epinephrine (accidental or therapeutic injection)-induced TS or pheochromocytoma-induced TS [14,16,31,33,46], where epinephrine elevation occurs in most of the cases [46]. Consequently, "epinephrine caused TS" could not explain the disease in about 50% of TS patients. Really, the apical sparing patterns of TS are underestimated in other TS populations where TS is triggered by all emotional and physical stressors. Sharkey et al.. [47] reviewed the left ventricular contraction patterns detected by CMR imaging in 95 patients where 79 patients (83%) classified as apical or mid-apical TS and 16 patients (17%) as mid-ventricular. Interestingly, of the 79 patients with apical or mid-apical, 33 patients (almost 35%) showed localized sparing of the most apical segment, tip-apical sparing. In such a case 49 out of 95 patients (52%) may be deemed as mid-ventricular TS in that study. Consequently, the evidences provided above make the epinephrine induced switch in signal trafficking hypothesis as a cause of TS highly unlikely.

8. Epinephrine may trigger takotsubo syndrome

Sufficient evidence for the absence of a direct causal relation between epinephrine and TS has been provided. However, TS has been induced in both animal models [44] and reported clinically in human[14]. As mentioned previously, Paur et al. [41] and Redfors et al. [44] could

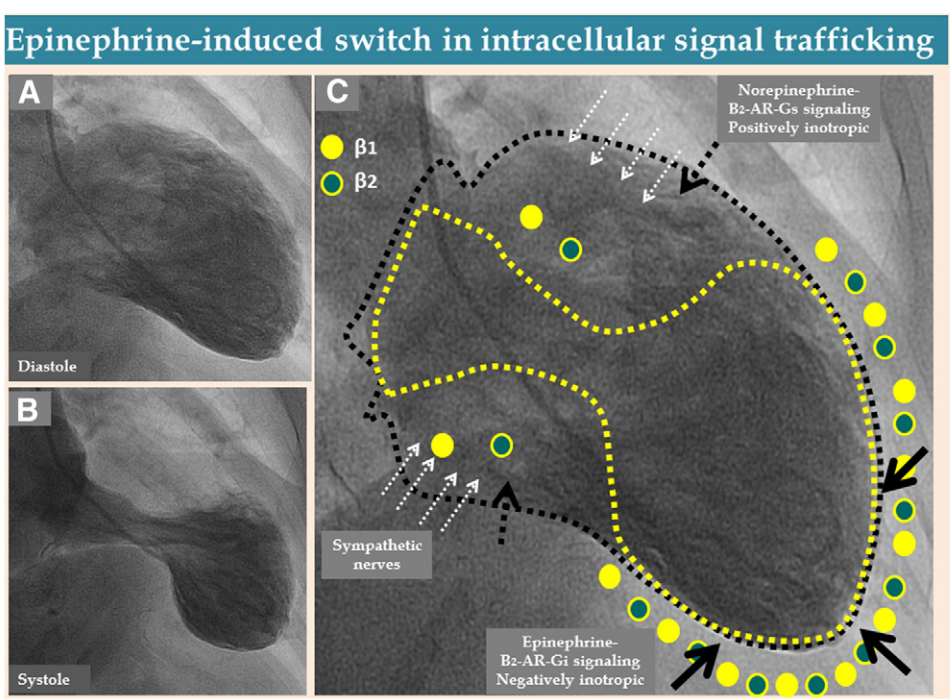

Fig. 5. Epinephrine-induced switch in signal trafficking hypothesis [13]: Mid-apical ballooning pattern in a patient with takotsubo syndrome (A, diastole, B, systole). C. Epinephrine β_2-AR-Gi signaling, negatively inotropic at the mid-apical segments of the left ventricle. Norepinephrine β_1-AR-Gs signaling, positively inotropic at the basal segments of the left ventricle.

induce TS in rats. Other investigators have demonstrated the feasibility of human in vitro TS model by using induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) [48,49]. Borchert et al. [48] provided evidence that catecholamine-treated TS-specific iPSC-CMs mimic features consistent with those found in individuals with TS. El-battrawy et al. [49] have performed an experimental analysis of high concentration of catecholamines on electrical properties in human iPSC-CMs and found that beta-estradiol has protective effects against catecholamine excess and hence reduction in estrogen levels. The same study also suggested that beta-blockers may be potential alternatives for the treatment of arrhythmias induced by catecholamine excess.

Moreover, tens of cases of epinephrine-triggered TS during therapeutic, accidental administration of epinephrine [14] or in disease condition, characterized by, among others, massive epinephrine elevation as pheochromocytoma [16], has been published. Abraham et al. reported on 9 cases of TS induced by intravenous administration of catecholamines and beta-receptor agonists where 6 cases were epinephrine-induced. Two reviews comprising of 33 cases [14] and 41 cases [33] of epinephrine-triggered TS have been published. Recently, Kido and Guglin reported on 157 of drug-induced TS where epinephrine was the most common drug inducing TS in 25 cases (15,9%) [50]. Pheochromocytoma-triggered TS [16,32] where epinephrine may also be involved has also been reported in tens if not hundreds of cases. Epinephrine-induced TS is characterized by a dramatic presentation where the clear majority of patients developed symptoms of hemodynamic disturbances immediately after the injection. In 17 of 20 cases, the symptoms or the hemodynamic disturbances started immediately, directly or shortly, within minutes, after epinephrine administration [14]. One third of the patients with epinephrine-triggered TS had basal (inverted) pattern of TS localization and almost half of the patients (48.5%) had apical sparing pattern of TS, which was more frequent than the apical type (42.4%) of TS localization [14]. This contrasts with other all-TS population, where only 2.2% had basal (inverted) [51]. The 33% of basal pattern of TS triggered by epinephrine is comparable to 31.5% of inverted TS triggered by pheochromocytoma reported by Agarwal et al. [32] and the 30% basal TS triggered by pheochromocytoma reported by Y-Hassan [16]. In epinephrine-triggered TS, STEMI-like ECG changes or T-wave inversions are usually found in the apical or mid-ventricular pattern of TS and the ST-depression or peaked upright T-waves are found exclusively in the basal pattern of TS [14]. Epinephrine-triggered TS is characterized by high complication rates (57.6%) in the form of heart failure, pulmonary edema, cardiogenic shock or arrhythmias [14]. Worth to mention here is that treatment with inotropic medications in patients with TS complicated by cardiogenic shock including that induced by epinephrine should be avoided because clinical studies have shown worse outcome in patients treated with catecholamines [5]. The rate of complications is significantly related to the accidental type and the dose (>1 mg) of epinephrine administration [14]. Ten of 11 patients (91%) who received epinephrine inadvertently developed complications compared with 4 of 20 patients (20%) who received epinephrine for therapeutic reasons ($p < 0.001$). Ten of 11 (91%) patients who received >1 mg epinephrine developed significantly ($p = 0.02$) more complications compared to 10 of 22 patients (45%) who received ≤1 mg (10 patients) or when epinephrine was administered as local anesthesia subcutaneously where the dose was therapeutic (12 patients). The complication rate is significantly higher in Epinephrine-triggered TS than that of all-TS population reported by Templin et al. [51] and other reported all TS populations [52]. Despite high rate of severe complications, the prognosis was good; all patients recovered with no in-hospital mortality recovered in the review of 33 patients by Y-Hassan [14] and only one death in the review of 41 cases by Nazir et al. [33]. Low in-hospital mortality rate (2.5%) was also reported in the 80 recently reviewed published cases with pheochromocytoma-triggered TS was [16]. The in-hospital mortality in all-TS population was 4.1% reported by Templin et al. [51].

9. Conclusion

Systematic review of the literature revealed that patients with TS have normal or mild-moderate elevation of plasma epinephrine. Substantial evidences argue against a direct causal link between epinephrine and TS. Epinephrine as any other physical stress factor may trigger TS.

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