Takotsubo-Syndrom

Das “gebrochene “ Herz

PGC Baden 4.– 5.5.2017

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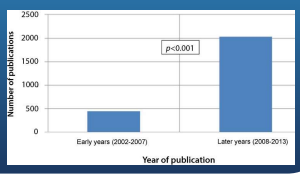
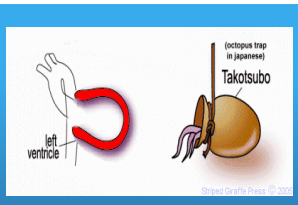
Erstbeschreibung 1990 durch Sate et al.

„Stunned myocardium with specific (tsubo-type) left ventriculographic configuration due to multivessel spasm“ Clinical Aspects of Myocardial Injury: From Ischemia to Heart Failure. Kagakuhyouronsya Co: Tokyo; 1990. pp. 56-64

Dote et al „Myocardial stunning due to simultaneous multivesselcoronary spasms; a review of five cases“ *J. Cardiol 1991; 21:203)*



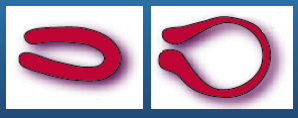
Otten, Neth. Heart J 2016, Sept. 24(9)



Häufigste Kontraktilitäts-störung:

„Apical ballooning“

(Tako = Oktopus, Tsubo = Flasche)



Normale Kontraktion Apical Ballooning

European Journal of Heart Failure (2016) **18**, 8–27
doi:10.1002/ejhf.424

REVIEW

Current state of knowledge on Takotsubo syndrome: a position statement from the task force on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology

Alexander R. Lyon[1,2,*], Eduardo Bossone[3], Birke Schneider[4], Udo Sechtem[5], Rodolfo Citro[6], S.Richard Underwood[1,2], Mary N. Sheppard[7], Gemma A. Figtree[8,9], Guido Parodi[10], Yoshihiro J. Akashi[11], Frank Ruschitzka[12], Gerasimos Filippatos[13], Alexandre Mebazaa[14], and Elmir Omerovic[15]

Heart Failure Association diagnostic criteria for Takotsubo syndrome

1. Transient regional wall motion abnormalities of LV or RV myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually[a] extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g. hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible electrocardiography (ECG) abnormalities (ST-segment elevation, ST depression, LBBB[b], T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e. disparity between the troponin level and the amount of dysfunctional myocardium present).[c]
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).[d]

Eur J of Heart Failure 2016

Pathophysiologie:

- *Pathogenese nicht vollständig geklärt*
- *Auslösend häufig Stress (emotional oder physisch)…*

➢ *Schädigung des Myokards durch erhöhte Katecholaminspiegel?*
(in 74% Gianni M. EHJ 2006, 27, 1523-1529)

Table 2. Plasma Catecholamine and Neuropeptide Levels.[a]

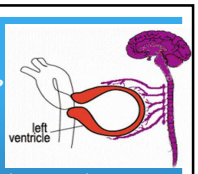
Variable	Patients with Stress Cardiomyopathy (N=13)			Patients with Killip Class III Myocardial Infarction (N=7)			Normal Value
	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	
	median (interquartile range)						
Catecholamine precursor (pg/ml)							
Dihydroxyphenylalanine	2859 (2721–2997)†	2495 (2386–2761)†	1656 (1065–2011)	1282 (1124–1656)	1203 (1193–1873)	907 (749–937)	1755‡
Catecholamines (pg/ml)							
Epinephrine	1264 (916–1374)†	1044 (733–1118)†	348 (180–559)	376 (275–476)	330 (220–385)	275 (220–311)	37‡
Norepinephrine	2284 (1709–2910)†	1573 (1235–2589)†	1142 (525–1252)	1100 (914–1320)	829 (727–914)	541 (516–660)	169‡
Dopamine	111 (106–146)†	77 (63–110)	56 (47–77)	61 (46–77)	61 (61–77)	38 (30–61)	15‡

Wittstein, NEJM 2005;352

➢ *Spasmen der epikardialen Koronargefäße ?*
(sehr selten d. Acetylcholin i.c. auslösbar)

Brain-Heart-Axis

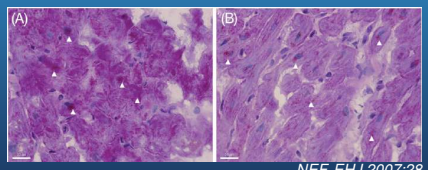
- *Störung der koronaren Mikrozirkulation ?*



Endomyokardiale Biopsien:

Interstitielle Infiltrate, hauptsächlich von mononukleären Lymphozyten und Makrophagen und „contraction bands" ohne Myozytennekrose

Elektronenmikroskopisch: zahlreiche intrazelluläre (Myozyten) Vakuolen und Glykogendepots, die sich in der Erholungsphase zurückbilden



NEF, EHJ 2007;28

Table 1 Triggers for secondary Takotsubo syndrome

Endocrine
e.g. Phaeochromocytoma, thyrotoxicosis (endogenous and iatrogenic), SIADH, Addisonian crisis, multiple endocrine neoplasia 2A syndrome, hyperglycaemic hyperosmolar state, hyponatraemia, severe hypothyroidism, Addison's disease, adrenocorticotropin hormone deficiency, autoimmune polyendocrine syndrome II
Neurological and neurosurgical
Acute neurosurgical emergencies (e.g. subarachnoid haemorrhage, acute head injury, acute spinal injury)
Acute neuromuscular crises, especially if involving acute ventilatory failure (e.g. acute myasthenia gravis, acute Guillain–Barré syndrome)
Epileptic seizures, limbic encephalitis, ischaemic stroke, posterior reversible encephalopathy syndrome
Respiratory
Acute exacerbation of asthma or COPD (especially with excessive use of inhaled beta2-agonists)
Acute pulmonary embolism
Acute pneumothorax
Obstetric, e.g. miscarriage, labour, emergency Caesarean section
Psychiatric
Acute anxiety attack/panic disorder
Attempted suicide
Drug-withdrawal syndromes
Electroconvulsive therapy
Gastrointestinal, e.g. acute cholecystitis, biliary colic, acute pancreatitis, severe vomiting, severe diarrhoea, pseudomembranous colitis, peritonitis

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Infection
Severe sepsis
Babesiosis
Cardiological
Dobutamine stress echocardiography
Radiofrequency arrhythmia ablation
Pacemaker implantation
Electrical DC cardioversion for atrial fibrillation
Post-cardiac arrest including ventricular fibrillation
Haematological
Blood transfusions
Thrombotic thrombocytopenic purpura
Surgical
Many cases have been reported during induction of general anaesthesia or during non-cardiac surgery or interventional procedures under local or general anaesthesia (e.g. cholecystectomy, hysterectomy, rhinoplasty, Caesarean section, radiofrequency liver ablation, radiotherapy, colonoscopy, difficult urinary catheterization, carotid endarterectomy)
Medication and illicit drugs
Epinephrine injection
Nortriptyline overdose, venlafaxine overdose, albuterol, flecanide, metoprolol withdrawal, 5-fluorouracil, duloxetine
Cocaine abuse

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Epidemiologie

- geschätzte 1,7 – 2,2 % aller Fälle mit STEMI,
  (Bybee KA, Am J Cardiol 2004;94)
- Überwiegend postmenopausale Frauen (80-100% weiblich, >95% älter als 50J) *Circulation, 2008,118*

Table. Patient Clinical and Laboratory Characteristics

	Tsuchihashi et al[1]	Kurowski et al[10]	Kurisu et al[2]	Sharkey et al[8]	Wittstein et al[12]	Inoue et al[11]	Salto et al[4]	Bybee et al[7]	Yoshida et al[15]	Akashi et al[3]
Subjects, n	88	35	30	22	19	18	16	16	15	13
Country	Japan	Germany	Japan	US	US	Japan	Japan	US	Japan	Japan
Series type	Retrospective	Prospective	Retrospective	Prospective	Prospective	Retrospective	Retrospective	Prospective	Prospective	Prospective
Age, y	67±13	72±9	70±8	65±13	61±15	76±8	71±9	71±12	72±7	73±10
Women, %	86	94	93	91	95	94	94	100	80	85
Preceding emotional stressor, %	20	42	17	86	100	11	. . .	38	40	31
Preceding stressor, %	43	42	17	14	. . .	39	100	44	40	69
Chest pain, %	67	. . .	67	91	95	72	100	69	87	54
ST-segment elevation, %	90	69	100	59	11	100	56	81	87	92
ST-segment elevation in precordial leads, %	85	. . .	97	59	. . .	100	. . .	81	. . .	92
Q waves, %	27	. . .	. . .	45	37	56†	. . .	31	7	. . .

Yoshihiro J. Akashi

Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy

N ENGL J MED 373;10 NEJM.ORG SEPTEMBER 3, 2015

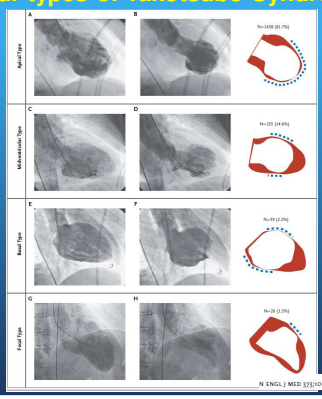
International Takotsubo Registry: 26 Centers in Europe and U.S.
Inclusion of 1750 pts. with Takotsubo-Syndrome

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Takotsubo Cardiomyopathy		Acute Coronary Syndrome
	Total Cohort (N=1750)	Matched Cohort (N=455)	Matched Cohort (N=455)
Female sex — no. (%)	1571 (89.8)	411 (90.3)	411 (90.3)
Age — yr	66.4±13.1	67.7±12.5	68.7±12.3
Coronary artery disease	245/1597 (15.3)	96/455 (21.1)	455/455 (100.0)
Neurologic or psychiatric disorder	714/1525 (46.8)	252/452 (55.8)	115/448 (25.7)

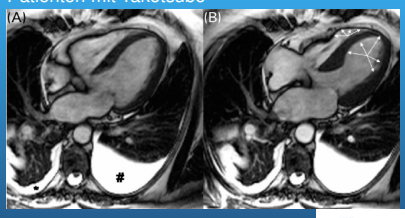
physical trigger: 36 %
emotional trigger: 27,7 %
both triggers: 7,8 %
any evidence trigger: 28,5 %

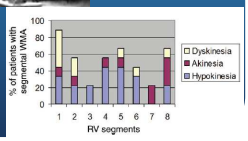
Four types of Takotsubo-Syndrom



Rechtsventrikelbeteiligung (Haghi, EHJ 27:2433-39, 2006)

- rechtsventrikuläre Wandbewegungsstörungen in 26% bei Patienten mit Takotsubo

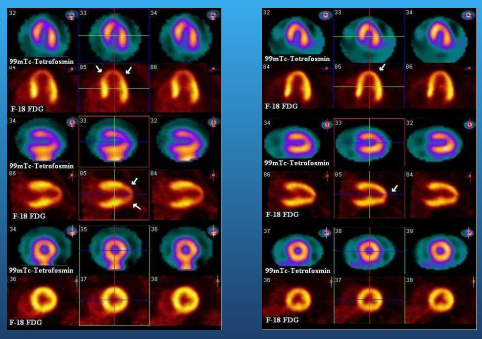




Myokardszintigraphie, PET:

- Myokardszintigraphie: erhaltene Perfusion
- PET: Myocardial stunning in der akuten Phase (inverse perfusion/metabolism mismatch), in der chron. Phase vitales Myokard

PET + Myokardszintigraphie



Akut

Follow-Up

Klinische Präsentation

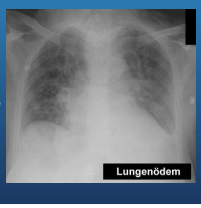
Ähnlich dem akuten Myokardinfarkt:

akuter Thoraxschmerz

NEJM: 75,9 % TS
89,6 % ACS

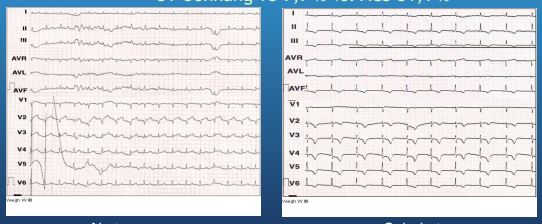
Dyspnoe

NEJM: 46,9 % TS
35,3 % ACS



EKG

- Veränderungen wie im Myokardinfarkt/ACS
- Häufig ST- Hebungen (34-56% i.B.der VW, Sharkey, Am J Cardiol 2008), T-Negativierungen, abnorme Q-Wellen
- Im Verlauf tief negative T-Wellen meist über der Vorderwand
- NEJM: Registry ST-Hebung TS 43,7 % vs. ACS 51,2 %
- ST-Senkung TS 7,7 % vs. ACS 31,1 %



Akut Subakut

Labor:

- Immer erhöhte Herzenzyme (Troponine, CK, CK-MB)
- Im Allgemeinen im Verlauf verhältnismäßig milde CK Auslenkung im Vergleich zum akinetischen Areal
- pBNP erhöht

NEJM: Registry: Factor x ULN (upper limit of the normal range)

median	*Troponin*	*TS 7,7*	*vs.*	*ACS*	*8,30*
median	*CPK*	*TS 0,85*	*vs.*	*ACS*	*1,12*
median	*BNP*	*TS 6,12*	*vs.*	*ACS*	*2,91*

Echokardiographie

Metaanalyse von Gianni, EHJ, 2006, 27

EF: 20 – 49%

Reference	Initial LVEF[a] (%)	Follow-up LVEF[a] (%)
Wittstein *et al.*[6]	20 (15–30)	60 (55–65)
Sharkey *et al.*[7]	29 ± 9	63 ± 6
Inoue *et al.*[8]	NR	NR
Ibanez *et al.*[9]	37 (20–50)	64 (58–75)
Akashi *et al.*[11]	42.2 (31–61)	64.4 (50–75)
Bybee *et al.*[12]	39.5 (32.8–48)	60 (50–68)
Kurisu *et al.*[13]	49 ± 12[b]	69 ± 12[b]
Matsuoka *et al.*[18]	48 ± 7[b]	72 ± 5[b]
Desmet *et al.*[5]	NR	NR
Ito *et al.*[19]	43.8 ± 4.3[b]	72.3 ± 4.5[b]
Ogura *et al.*[20]	NR	NR
Abe *et al.*[21]	NR	NR
Tsuchihashi *et al.*[22]	41 (10–62)	64 (44–88)
Kawai *et al.*[2]	NR	76 (61–86)

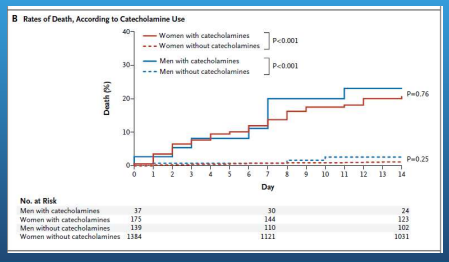
- Registry: TS EF 41,1 % ± 11,8 vs. ACS 51,5 ± 12,3

Therapie:

- MI-Therapie bis zur definitiven Diagnosesicherung!
- keine gesicherten Daten zu optimaler Therapie und Dauer der Therapie
- Betablocker, ACE-Hemmer, Diuretika/ Hydratation, ASS, Anxiolyse, Stressmomente beseitigen

Therapie:

- **Cave: Katecholamine**



Multivariate Analyse „International Takotsubo Registry"
Templin C, N Engl J of Medicine 373:27, 2015

Therapie:

- keine Inotropika bei LVOT-Obstruktion !!
  - → bei ausgeprägter Hypotension: vorsichtig alpha-Agonisten (Phenylephrin) Neosynephrin ®-Amp. a 1ml
  - → Levosimendan ?
  - → Vasopressin ?
- Evt. veno-arterielle ECMO („bridge to recovery“)

Therapie

Registry:
ACE-Inhibitors/ARB: improved survival at 1 year (P = 0,001)
Betablocker: no evidence of any survival benefit (P = 0,53)

Registry: 32,5 % der Patienten mit Betablocker entwickeln Rezidive, 57 Patienten mit Rezidiv → 29 waren auf Betablocker

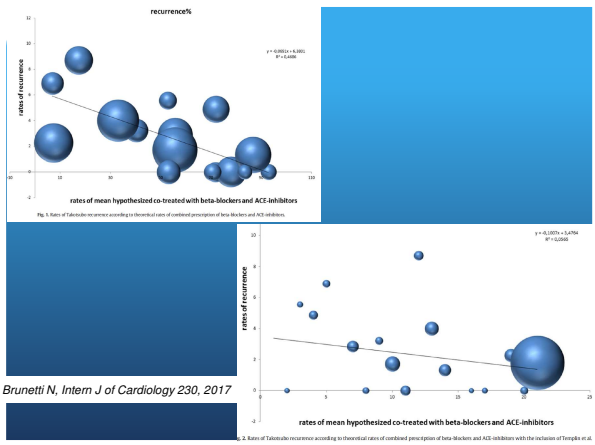
Betablocker: not effective in preventing takotsubo

Combined therapy with beta-blockers and ACE-inhibitors/angiotensin receptor blockers and recurrence of Takotsubo (stress) cardiomyopathy: A meta-regression study *International Journal of Cardiology 230, 2017*

Natale Daniele Brunetti [a,*], Francesco Santoro [b], Luisa De Gennaro [c], Michele Correale [d], Antonio Gaglione [e], Matteo Di Biase [e], John E. Madias [f,g]

Characteristics of studies included in the meta-regression analysis.

Study	Sample size	Rates of prescription in observational studies					Recurrence rates
		Beta-blockers	ACE-inhibitors/ARB	Minimal theoretical combined	Maximal theoretical combined	Mean theoretical combined	
Traulle	14	100%	93%	93%	93%	93%	0%
Previtali	18	72%	67%	39%	67%	53%	6%
Eshtehardi	41	80%	83%	63%	80%	72%	5%
Spedicato	29	100%	7%	7%	7%	7%	7%
Mhmoud	32	100%					0%
Regnate	70	77%	67%	44%	67%	56%	3%
Teh	23	74%	96%	70%	74%	72%	0%
Primtshofer	31	55%	71%	26%	55%	40%	3%
Parodi	116	70%	72%	41%	70%	56%	2%
Samardhi	52	85%	87%	71%	85%	78%	0%
Maekawa	46	46%	35%	0%	35%	17%	9%
Nunez-Gil	100	52%	62%	14%	52%	33%	4%
Cacciotti	75	89%	95%	84%	89%	87%	1%
Vriz	25	80%					20%
Shama	12	83%	100%	83%	83%	83%	0%
Showkathali	17	76%	88%	65%	76%	71%	0%
Pullara	26		96%				8%
Tsuchihashi	88	18%	15%	0%	15%	7%	2%
Herrting	32	63%	81%	44%	63%	53%	0%
Templin	1533	78%	79%	57%	63%	60%	2%



Brunetti N, Intern J of Cardiology 230, 2017

Table 3 In-hospital and long-term outcome of Takotsubo syndrome

Complication/outcome	Frequency
Acute complications	
Right ventricular involvement	18–34%
Acute heart failure	12–45%
LV outflow tract obstruction	10–25%
Mitral regurgitation	14–25%
Cardiogenic shock	6–20%
Arrhythmias	
Atrial fibrillation	5–15%
Ventricular arrhythmias	4–9%
Bradycardia, asystole	2–5%
Thrombus formation	2–8%
Pericardial tamponade	<1%
Ventricular wall rupture	<1%
In-hospital mortality	1–4.5%
Recurrence	5–22%
5-year mortality	3–17%

International Registry

	TS	ACS
Cardiogenic shock	9,9 %	10,5 %
In-hospital mortality	4,1 %	5,3 %

NEJM,373:10, 2015

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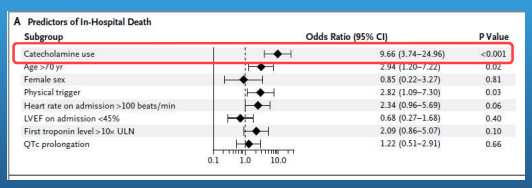
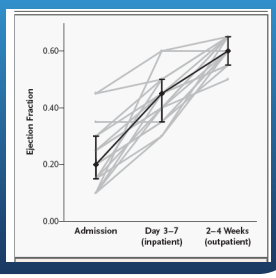


Multivariate Analyse „International Takotsubo Registry“
Templin C, NEJM 373:27, 2015

Prognose:

- **Gut:** komplette Erholung der LV-Funktion innerhalb von 1-4 Wochen



Wittstein, NEJM 2005;352