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ORIGINAL ARTICLE

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Myocardial contraction bands

Definition, quantification and significance in forensic pathology

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Abstract Pathological contraction bands affecting myocardial cells are observed in many different human conditions and in different experimental models. Their morphology was defined long ago but we need to understand the pathogenesis and functional meaning. A distinction between different histological forms of contraction bands and their quantification in a large spectrum of human diseases (262 cases) and a normal population sample where death was due to various types of accidental death (170 cases) produced the following conclusions: 1) The term "contraction band necrosis", as used presently, is ambiguous and should be reserved for a specific morpho-functional entity induced experimentally by intravenous catecholamine infusion and seen in equivalent human cases with pheochromocytoma. 2) In human pathology it may represent a sign of adrenergic stress linked with malignant arrhythmia/ventricular fibrillation. 3) Beyond a histological threshold of 37 ± 7 foci and 322 ± 99 myocells/100 mm^2, the lesion may indicate sympathetic overdrive in the natural history of a disease and associated arrhythmogenic supersensitivity. 4) The detection of few pathological contraction bands in normal subjects in some types of accidental death correlates with the survival time, suggesting an agonal adrenergic stimulation to promote the cardiac pump.

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Introduction

Myocardial "contraction band" changes surrounding an acute infarct were described long ago [1]. Many terms, such as anomalous contraction bands, focal myocytolysis, focal myocarditis, myofibrillar degeneration, infarct-like myocardial necrosis, myocytolysis with major contraction bands, myofibrillar degeneration, contraction band necrosis and coagulative myocytolysis or Zenker necrosis have been used to describe this change [2, 3, 4].

Contraction band necrosis is a marker of cell death and can be identified a short time after irreversible myocyte injury [5]. Since contraction band necrosis is associated with catecholamine excess, it may generally occur in all those different conditions resulting in alterations of the interaction between calcium and catecholamines [6, 7]. Contraction band necrosis has been associated with coronary occlusion [8], resuscitation attempts [9], drowning [10], intracranial haemorrhage [11], sudden cardiac death [12] and a wide variety of drugs [13].

In the literature a quantitative and systematic study of the lesion comparing its occurrence in different and unrelated conditions is lacking. In the present study the frequency and quantification of pathological contraction bands seen in a large spectrum of diseases and types of accidental deaths in normal subjects are described and the significance of the findings are discussed.

Material and methods

From 1986 a systemic and quantitative protocol to compare the main pathological variables found in the heart in different diseases and normal controls dying from various types of accidental death was adopted at our Institutes [14]. In this study the frequency and extent of contraction band necrosis was investigated in several pathological conditions, the selective criteria and main parameters of which are given in Table 1.

Table 1 Criteria of selection and main parameters of the different groups studied

Groups	Total cases	Men/ Women	Age (years)	Heart weight (g)	Death in or out of Hospital		Survival		Resuscitation attempts		Selection criteria
					Out	In	(min)	(days ± SE)	Yes	No	
Coronary	25	21/4	61 ± 3	562 ± 25	25	–	5/60	–	13	12	Sudden/unexpected death. All had different grades of coronary atherosclerosis. No history of coronary heart disease
Chagas	34	26/8	49 ± 2	464 ± 28	34	–	< 5	–	–	34	Sudden/unexpected death, serum positive for Chagas' disease. No or minimal coronary atherosclerosis. No history of heart disease
Brain haemorrhage (BH)	27	6/21	59 ± 2	427 ± 19	–	27	–	6 ± 2	In hospital	–	No heart disease. Haemorrhage due to rupture of berry aneurysm
Transplanted hearts (TRH)	46	39/7	49 ± 1.5	419 ± 19	–	46	–	391 ± 89	In hospital	–	Death occurred within first week to more than 1 year
Acquired immuno deficiency syndrome (AIDS)	38	33/5	31 ± 2	368 ± 11	–	38	–	289 ± 39	In hospital	–	Death due to opportunistic infections
Congestive heart failure (CHF)	144[a]	130/14	47 ± 1	473 ± 10	–	–	–	–	–	–	Irreversible end-stage failure, clinically identical in coronary heart disease (63), dilated cardiomyopathy (63), chronic valvulopathy (18) patients
Cocaine-associated death (CA)	26	20/6	35 ± 1	351 ± 10	–	26	–	8 ± 2	In hospital	–	Cocaine-associated death. No cardiac disease. No or minimal coronary atherosclerosis
Accidental death (AD)	92	78/14	42 ± 2	364 ± 7	92	–	5/180	–	–	92	In all these cases non-pathological findings at autopsy
Head trauma (HT)	45	37/8	42 ± 3	364 ± 10	45	–	5/60	–	–	45	No or minimal coronary atherosclerosis or myocardial fibrosis
Electrocution (E)	21	21/0	36 ± 4	347 ± 9	21	–	< 5	–	–	21	Negative toxicological tests for poisoning but positive for carbon monoxide intoxicatio
Carbon monoxide (CO)	26	20/6	48 ± 3	375 ± 14	26	–	> 180	–	–	26	None received medical attention. All died out of hospital

[a] Hearts excised at surgery

For examination of the hearts, the whole organ was washed, weighed and fixed for 24 h in 10% buffered formalin. The subepicardial coronary arteries and main branches were then cross-sectioned at 3 -mm-intervals and each segment with wall/luminal changes was examined histologically. Subsequently, the whole heart was cut in 1 -cm-thick slices from apex to base and one superior and one inferior slice was examined histologically by sampling the entire wall of anterior, lateral and posterior left and right ventricles and anterior and posterior interventricular septum. However, in the cases of accidental death and cocaine-associated death, myocardial samples were limited to four specimens taken from the whole anterior left ventricle.

Due to the surgical procedure the weight of an excised heart at transplantation included the ventricles only, but for comparative purpose we added to this weight a calculated atrial weight (actual heart weight × 100/75) which corresponded to one-quarter of the total muscle mass [15].

The lumen reduction of coronary arteries was expressed as a percentage of lumen diameter calculated from plastic casts of normal vessels [3].

Quantitative analysis

In all hearts the area of each histological myocardial section (excluding epi- and endocardium) was measured in pixels by an image analysis system (Vidas, Zeiss, Germany) and converted to square millimetres through a calibration procedure using a reference system. Both the numbers of foci and myocells with pathological contraction bands (see below) were normalised to 100 mm^2. This lesion may range from one focus formed by thousands of myocells to many foci of one or a few myocells per focus.

Definitions

Physiological contraction bands

The myocardial cell is structured to beat from early fetal life to death, the cause of which is often the result of its primary arrest. The cell is composed of myofibrils, subdivided into sarcomeres (the functional unit) limited by thin Z-lines. The parallel order of myofibrils gives the characteristic physiological bands seen histologically and which, according to the "sliding theory" of actin and myosin filaments, undergo a change in relation to the contraction-relaxation cycle. The biochemical key of this cycle is the Ca^{++} pump with rhythmic to-and-fro transfer of this ion from the troponin-tropomyosin complex of contractile proteins (contraction) to the sarcoplasmic reticulum (relaxation). In the physiological range of myocardial cell activity no modification of Z-lines occurs.

Contraction bands necrosis and its relationship to the contraction-relaxation cycle

Histologically, this form of myocardial necrosis is characterised by irreversible hypercontraction of the myocell with a breakdown of the whole contractile apparatus with markedly thickened Z-lines and extremely short sarcomeres. This breakdown varies from irregular, pathological and eosinophilic cross-bands constisting of segments of hypercontracted or coagulated sarcomeres, to a total disruption of myofibrils, the whole cell assuming a granular aspect without visible clear-cut pathological bands [16].

Contraction band necrosis (CBN), as defined above, is reproduced experimentally by intravenous infusion of catecholamines, is not an ischemic change [17] and is observed in many human pathologies [2, 3]. It ranges from foci formed by one or a few myocells to large zones of myocardium in the absence of interstitial/intermyocellular haemorrhage. The following evolving pathology of this necrosis can be distinguished:

a) Hypercontraction/cross-bands as an early change

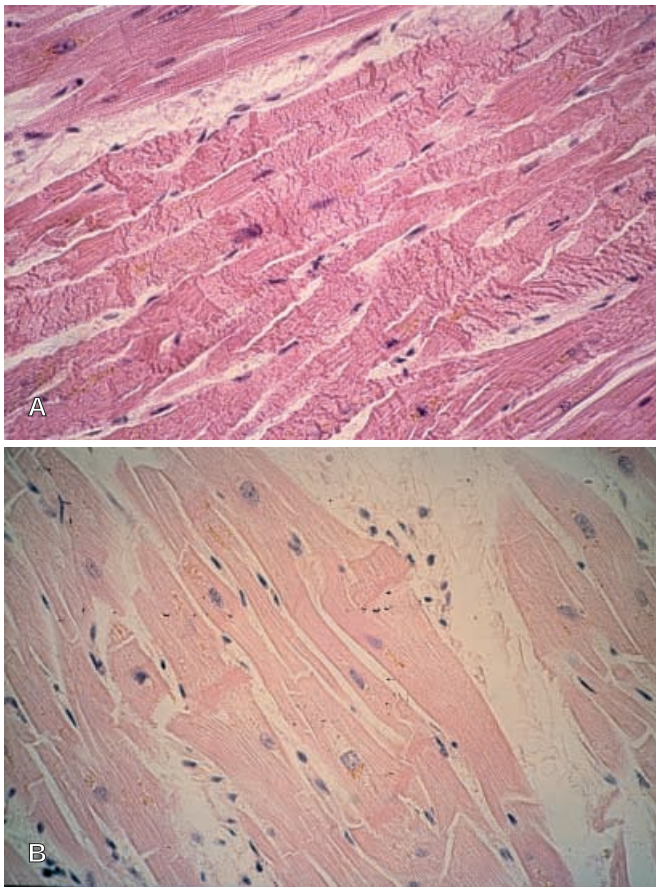

Fig. 1 A, B Contraction band necrosis. **A** Pancellular lesion with fragmentation of hypercontracted myofibrils and band formation of hypercontracted or coagulated sarcomeres (H&E × 250). **B** Paradiscal lesion formed by about 15 hypercontracted sarcomeres without myofibrillar rhexis. Both lesions are visible within 5–10 min after intravenous catecholamine infusion in the dog. Note the absence of oedema, haemorrhage and myofibre vacuolisation (H&E × 250)

b) Progressive destruction of myofibrillar remnants associated with monocytes/macrophages leading to an alveolar pattern formed by empty sarcolemmal tubes infiltrated by macrophages loaded by lipofuscin
c) A healing phase with progressive collagenisation ending in a fibrous scar (Fig. 1) [18, 19].

We note that an opposite pattern of necrosis is seen when myocells arrest in irreversible relaxation and are stretched by the interventricular pressure with an increased length of both sarcomeres and nuclei, the latter becoming intensely basophilic. This irreversible relaxation ends in necrosis when a reduced nutritive blood flow persists for more than 20 min. This infarct necrosis has characteristic histological features without oedema, vacuolisation, haemorrhage and contraction bands. A registered order of sarcomeres is still visible in necrotic myocellular remnants at the end of healing (Fig. 2) [2, 3].

These two forms of myonecrosis may be reversible before they evolve fully and can be focal or global. Infarct necrosis is mainly monofocal and regional, and is only exceptionally global. Contraction band necrosis is plurifocal and only in a rare condition is it global e.g. "stone heart" [20].

The term sudden unexpected death refers to apparently normal subjects, enjoying their usual life-style, who are not under medical care, have no history of diseases to which death could be related and who died out-of-hospital. Accidental death means a rapid demise

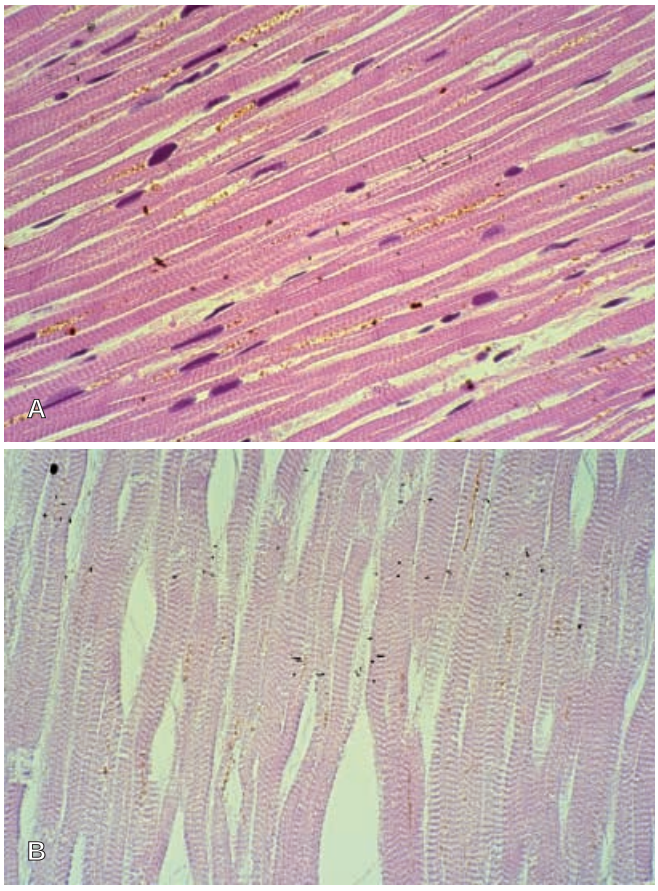

Fig. 2 A, B Early infarct necrosis. **A** Stretching of flaccid paralysed myofibres by intraventricular pressure with elongation of nuclei and sarcomeres, a change visible within 1 h in experimental coronary occlusion. Note the absence of oedema, haemorrhage, vacuolisation and pathological contraction bands (H&E × 250). **B** Infarct of 25 days almost completely healed. Despite some destaining of this old necrotic tissue, elongated sarcomeres in registered order in absence of contraction bands and vacuolisation are still visible. (H&E × 250)

out-of-hospital following trauma, wounds, poisoning, intoxication or any equivalent [3]. Silent means a disease diagnosed post-mortem, but unrecognised clinically because a lack of symptoms.

Statistics

Data are expressed as mean values ± 1 standard error. To assess statistically significant differences, Student's *t*-test for paired or unpaired data or one-way analysis of variance and post hoc Scheffe's test for continuous variables and the λ^2-test for discrete variables were used where appropriate. Continuous variables not normally distributed were analysed non-parametrically using Kruskal-Wallis analysis of variance for more than two groups and Mann-Whitney test for two groups. A measured probability value of $p < 0.05$ was considered significant.

Results

Frequency and extent of contraction band necrosis

In the accidental death groups the frequency and extent of this lesion were significantly less ($p < 0.01$) than in other groups (Table 2). In particular, pathological contraction bands were practically absent or minimal in normal, non-resuscitated subjects who died rapidly (< 5 min) or from CO intoxication. The maximal frequency of lesions (100%) was observed in Chagas cases followed, in diminishing order, by intracranial haemorrhage (89%), hearts excised at transplantation for congestive heart failure (87%), transplanted hearts (85%), sudden unexpected coronary deaths (76%) and AIDS (66%) cases (Table 2).

At histological examination 4 amongst the 25 cases in the sudden unexpected coronary death group proved to have a "silent" acute myocardial infarction with an age ranging from 24 h to 10 days and a size from less than 10% to 30% of the ventricular mass. These hearts showed the greatest extent per 100 mm^2 of CBN (Table 2). In previous studies the extent of CBN was not measured specifically but reported as involving a variable and often large amount of myocardium unrelated to the size of the infarct [21, 22, 23]. To establish the extent of CBN in coronary death without infarcts we excluded these four cases. The number of foci of CBN was significantly higher ($p < 0.0001$) in transplanted hearts in respect of congestive heart failure. When only groups with examination of different heart locations were considered, transplanted, heart coronary, intracranial haemorrhage groups ($p < 0.0001$) and resuscitated versus non-resuscitated coronary subjects ($p < 0.0001$) showed a significant higher number of foci/myocells with CBN. Except for silent infarct cases, the number of foci and necrotic myocells ranged in values that were compatible with a minimal loss of contractile tissue. In order to have diagnostic criteria on the "pathological" extent of CBN, all data of the groups with the highest frequency of this lesion, i.e. coronary, Chagas, brain haemorrhage, transplant groups, were combined and compared with the assembled data of the accidental death groups. Hearts excised at transplantation were excluded since the cardiac arrest was surgical and therefore without lesions due to an agonal period and related treatment. Foci and myocells in the first group were 37 ± 7 and 322 ± 99, both significantly higher ($p < 0.0001$ and $p < 0.05$ respectively) than the figures (7 ± 2 and 19 ± 5) found in the second one.

Age of lesions. In all accidental death cases only early lesions, i.e. pathological bands, were found. In the other groups a substantial frequency of older, i.e. alveolar and healing stages were documented (Table 2). It must be stressed that in most cases older lesions were associated with the earliest ones.

Location. In all groups except transplanted human hearts, the lesion prevailed in the left ventricle ($p < 0.01$) followed by the right one and interventricular septum (Table 3). No difference was noted in different areas (anterior, lateral, posterior) of the ventricles.

Contraction band necrosis versus other parameters. The frequency and extension of the lesion could not be correlated with age, gender, heart weight, the presence or absence of severe (> 70% lumen-diameter reduction) coro-

Table 2 Frequency and extension of contraction band necrosis in the left anterior ventricle

Source	Contraction band necrosis						
	Total cases	Present	Foci[a]	Myocells[a]	Histological stages of CBN		
					Cross band	Alveolar	Healing
Coronary	25	16	42 ± 16	881 ± 493	3	13	3
+ Infarct silent[a]	4	3	31 ± 16	3564 ± 2225	1	2	1
No infarct	21	13	44 ± 19	263 ± 112	2	11	2
No resuscitation	10	5	23 ± 8	181 ± 83	1	5	–
Resuscitation	11	8	58 ± 31	313 ± 177	1	6	2
Chagas	34	34	4 ± 2	47 ± 35	8	16	10
BH	27	22	31 ± 9	106 ± 45	13	9	2
< 1 day survival	14	11	17 ± 6	30 ± 10	9	3	–
> 1 day survival	13	11	44 ± 17	182 ± 84	4	6	2
TRH	46	36	50 ± 14	304 ± 72	14	17	8
AIDS	38	16	7 ± 3	22 ± 10	19	6	–
CHF	144	90	3 ± 1	19 ± 4	65	25	36
Cocaine	26	9	4 ± 1	12 ± 5	11	–	–
Head trauma	45	9	10 ± 6	23 ± 11	9	–	–
< 1 h survival	26	1	0.5	35	1	–	–
> 1 h survival	19	8	12 ± 6	21 ± 12	8	–	–
Electrocution	21	1	8	46	1	–	–
CO	26	3	1 ± 0.5	5 ± 2	3	–	–

[a] The four cases with silent acute myocardial infarction excluded when extent was calculated in coronary group

Table 3 Location of contraction band necrosis in different groups (*LV* left ventricle free wall, *RV* right ventricle free wall, *IVS* interventricular septum)

Source	Contraction band necrosis								
	Total case	Present	LV	LV + RV	LV + IVS	LV + RV + IVS	RV	RV + IVS	IVS
Coronary	25	19	1	2	4	11	1	–	–
Chagas	34	34	6	10	2	14	–	–	2
BH	27	24	3	1	6	14	–	–	–
TRH	46	39	2	1	2	31	1	1	1
AIDS	38	25	6	2	2	8	5	–	2
CHF	144	126	20	18	9	67	5	4	3

Cocaine and AD groups excluded because sampling limited to anterior LV (see methods)

nary stenosis (Table 4), mural or occlusive thrombi at any level of the coronary tree or with resuscitation therapy in the agonal period.

Discussion

Different forms of pathological contraction bands in respect to function

Use of the term "band" may generate confusion. As indicated above we distinguished physiological bands of the contraction cycle, pathological bands which, as with any pathological event, may be either reversible or irreversible and artifactual bands.

Hypercontraction of the myocells is characterised by extremely short sarcomeres that are shorter than their theoretical length (1.5 μm). This change is associated with marked thickening of the Z-lines. Such a thickening, sometimes called "contraction bands" or CBN is, with the artifactual exception noted below, a pathological finding and is not seen in normal contraction where there is no modification of the Z-lines. The significance of pathological contraction bands is unknown in particularly with regards to the question whether or not the change is reversible. In the literature contraction bands refer to a specific histological pattern which is the result of fragmentation of hypercontracted myofibrils into eosinophilic bands. This myofibrillar rhexis is probably due to the mechanical, rhythmic action of the normal contracting myocardium which surrounds rigid hypercontracted elements and may range from a few contraction bands to total granular destruction of myofibrils. This pancellular lesion is frequently associated with a paradiscal lesion without rhexis of the myofibrillar apparatus possibly because the major part of the myocell maintains its normal structure and function. It is still unclear if paradiscal lesions transform into pancellular ones or may revert to normal. Both lesions are reproduced

Table 4 Number of foci (*F*) and myocells (*M*) of contraction band necrosis

Group	Total	Maximum lumen diameter reduction									
		0–50%		51–70%		> 70%		Mono[b]		Multiple	
		F	M	F	M	F	M	F	M	F	M
Coronary[a]	21	24 ± 6	108 ± 27	6	10	30 ± 14	223 ± 61	6	10	29 ± 13	208 ± 57
Chagas	34	2 ± 1	19 ± 7	16	274	–	–	16	274	–	–
BH	27	26 ± 9	84 ± 32	12 ± 7	25 ± 16	41 ± 24	55 ± 33	93	131	24 ± 7	53 ± 20
TRH	46	41 ± 11	249 ± 47	3 ± 1	95 ± 57	32 ± 13	675 ± 288	0.2	9	33 ± 13	273 ± 69
CHF	144	2 ± 1	13 ± 4	1 ± 0.2	5 ± 2	1 ± 0.2	11 ± 3	3 ± 1	26 ± 10	2 ± 0.4	10 ± 2
Ischemic	63	1 ± 1	25 ± 14	1 ± 0.2	4 ± 1	1 ± 0.2	12 ± 3	5.07	49	1 ± 0.2	11 ± 2
Dilated	63	2 ± 1	14 ± 5	1 ± 0.4	8 ± 5	0.1 ± 0.04	0.4 ± 0.2	2 ± 1	18 ± 9	2 ± 1	12 ± 4
Valvulopathy	18	2 ± 1	5 ± 2	0.8	3	0.2	1	–	–	1 ± 0.4	3 ± 1
AIDS	38	4 ± 2	14 ± 6	0.2	0.3	–	–	8 ± 7	21 ± 13	2 ± 2	3 ± 2
Total	314	14 ± 3	75 ± 14	3 ± 1	27 ± 11	10 ± 3	79 ± 24	12 ± 6	44 ± 18	10 ± 2	64 ± 12

[a] Four silent acute infarct cases excluded
[b] Mono, cases with only one vessel > 70% stenosis; multiple, two or more vessels with > 70% stenosis

by intravenous catecholamine infusion in dogs [16] and are found in all conditions we have reported. The paradiscal lesion was described by other authors as the zonal lesion [24, 25] and was prevented by a beta-blocking agent [26]. In hypercontraction damage we should also consider two other variants, i.e. reflow or reperfusion myocardial necrosis which develops after temporary ischemia and is characterised by extensive CBN plus midzone, interstitial haemorrhage [27], and cutting edge hypercontraction, an artifact seen at the margin of samples taken from living myocardium (e.g. biopsy and hearts excised at transplantation), i.e. a 0.2–0.5 mm layer of "retracted portion" of myocells with very short sarcomeres and thickened Z-lines without rhexis [16]. We also note that contraction band changes develop in vivo following trauma, e.g. cardiac massage.

Quantification

Contraction band necrosis as a diagnostic tool

Post-mortem findings are too often insufficient to explain the death and its cause. For instance, we may make a diagnosis of sudden coronary death based only on the presence of severe atherosclerotic coronary artery stenosis, despite the well documented fact that the latter frequently coexists with a non-ischemic myocardium [3]. The finding of CBN, even if microfocal, could be an important histological signal for interpreting the cause of death and the natural history of a disease in any single patient. In particular, in rapid death after the onset of a myocardial infarct undetectable histologically [28, 29, 30, 31], it could be the marker explaining cardiac arrest as secondary to adrenergic stress. However, one must remember that in people who die suddenly and unexpectedly, the frequency of an infarct is about 20% as shown in resuscitated and electrocardiographically monitored patients [3]. Therefore, finding foci of catecholamine damage per se in the heart of a case of sudden death within 6 h, does not absolutely confirm the presence of an underlying myocardial infarct [3, 32]. The obvious need is to discriminate between CBN resulting from pre-terminal stimuli and its presence as a histological sign of adrenergic overdrive during the course of a disease. A significant variability of this lesion in different normal and disease patterns exists. For instance, a negative finding was seen in CO intoxication, whether accidental or suicidal, suggesting, an anti-adrenergic effect of lethal anoxia despite a longer survival period. Only if reoxygenation is restored do contraction bands form without interstitial haemorrhage [33]. In other words, we need to know the frequency, extent and stages of this lesion to interpret both the natural history of a disease and the mode of death.

Significance

Contraction band necrosis is not an ischemic lesion

In the literature CBN has been considered an ischemic change since it is found associated with myocardial infarction and is reproduced by experimental reperfusion. This impression may have been induced by animal models of permanent and temporary coronary occlusion. From experience with the dog, a coronary occlusion of the left circumflex branch of 60 min duration produces a small subendocardial infarct characterised by stretched myocells with prominent I-bands. However when the coronary occlusion lasts only 40 min followed by 20 min reflow, the histological pattern transforms into typical CBN that was interpreted as ischemic [34]. In further experiments by prolongation of occlusion and/or reperfusion time, transmural (wavefront phenomenon) myocardial changes mainly formed by CBN associated with marked interstitial haemorrhage were obtained [27, 35].

A dilemma, therefore, is whether CBN is synonymous with a myocardial infarction or not. In 200 consecutive fatal acute infarcts consisting of 100 Italian [21] and 100 Canadian [22] cases and in 208 selected cases of sudden unexpected coronary death [23], interstitial-intermyocellular haemorrhage was never seen within infarct necrosis in the absence of cardiac wall rupture yet extensive, non-haemorrhagic CBN was always associated with a myocardial infarction irrespective of its size. Furthermore, the experimental wavefront phenomenon and expansion of previous infarct necrosis were never observed. This is in contrast to the belief that CBN is a consequence of reperfusion in general or to a temporary vascular spasm [36]. The question is how many times reperfusion happens in human pathology. Extensive CBN associated with massive interstitial-intermyocellular haemorrhage can be seen in post-cardiac surgery as circumferential haemorrhagic necrosis [37] following resuscitation manoeuvres and in certain instances of myocardial reperfusion. At present thousands of patients are reperfused without any complications, by vein graft by-pass, fibrinolysis and percutaneous intraluminal coronary angioplasty. Patients with an acute myocardial infarction, treated with fibrinolytic agents associated or not with balloon angioplasty, all had a haemorrhagic necrosis, not only confined in the central necrotic zone as in experimental reflow necrosis. In contrast, patients treated by balloon angioplasty alone had an anaemic infarct. The conclusion is that when haemorrhaging occurs it is related to the effects of pharmacological agents rather than a direct, mechanical coronary reflow [38]. In a review of 99 acute infarct cases treated by fibrinolytic agents, 43% had an haemorrhagic infarct. The central infarcted zones showed coagulative necrosis and in haemorrhagic infarcts associated with cardiopulmonary bypass or aortocoronary by-pass grafting, a clear-cut distinction between the size of infarct necrosis and the size of contraction band necrosis was not made [39], a point which need further investigation to clarify what a haemorrhagic infarct means after reperfusion in humans.

The concept that CBN is not an ischemic but rather a result of direct catecholamine toxicity, is based on experimental catecholamine infusion. The lesion is visible within 5–10 min of perfusion in the presence of normal vessels [15] and unrelated to ischemia [16]. Its presence in acute coronary syndromes is probably due to catecholamines released within the myocardium as a reflex response [40] to regional asynergy of the infarcted or preinfarcted zone, a hypothesis that is supported by the abolishment of contraction bands and ventricular fibrillation with beta-blocking agents in experimental myocardial infarction [41] and in reperfusion necrosis. The intramyocardial release of catecholamines may result from mechanisms other than asynergic myocardium any time the cardiac nerves are involved, e.g. inflammation around nerves of the tunica media of an atherosclerotic plaque [3, 42]. They may trigger a catecholamine myotoxicity linked with ventricular fibrillation and acting through free-radical mediated lipid peroxidation with intramyocellular Ca^{2+} influx [43, 44, 45]. An increase of noradrenaline in the interstitial fluid of an ischemic myocardium has been documented [46]. Contrary to the general opinion that excess catecholamines produce cardiotoxicity mainly through binding to adrenoceptors, there is increasing evidence that catecholamine-induced deleterious actions may also occur through oxidative mechanisms. Recent studies have shown that oxidation of catecholamines results in the formation of highly toxic substances such as aminochromes (e.g. adrenochrome) and free radicals and by virtue of the latter's actions on different types of heart membranes, they cause intracellular Ca^{2+} overload and myocardial cell damage [47].

Contraction band necrosis in forensic pathology

The present study is the first attempt to profile the natural history of CBN by its quantification in different human conditions. The frequency of this lesion ranged from a minimum of 8% in instantaneous accidental deaths in normal subjects who died following head trauma, to a maximum of 100% in acute myocardial infarction. A similar trend was observed in terms of the number of foci and myocells per mm^2 (Table 2). Its presence in normal subjects or patients with longer survival periods is probably related to agonal or pre-terminal sympathetic stimuli to improve contraction, as suggested by reoxygenation after CO intoxication [33]. However, in many conditions, the frequency and extent of CBN indicate an adrenergic role in the natural history of these diseases, e.g. ischemic heart disease [3], Chagas' heart disease [48], intracranial brain haemorrhage [11] and congestive heart failure [49, 50]; all diseases in which there is a general consensus for a sympathetic overtone. In other words, "sympathotonic" prone individuals may have an "adrenergic crisis" any time a physical and/or psychological stress occurs, which explains the high variability among subjects of the same group. A concept supported by the presence in the same heart of all stages (e.g. cross bands, alveolar healing) of the lesion particularly in excised hearts at transplantation. The latter are a

unique model since agonal stimuli and reanimative, terminal therapeutic procedures are absent. It is noted that in experiments, hearts excised in control animals did not show contraction bands of any type [15]. The early CBN in human excised hearts may be related to presurgical adrenergic stress in patients already with increased sympathetic overtone. Accordingly the threshold for a diagnosis of sympathetic stress seems to be a number of foci and myocells/100 mm^2 with the range of those found in the previously mentioned diseases (Table 2) and the presence of foci of CBN of any stages. The significantly higher extent of this lesion in sudden unexpected coronary death cases with resuscitation attempts, seems more likely to be due to a longer survival rather than to any iatrogenic effects. In fact, the frequency and extent of early changes were similar in treated and non-treated subjects, all showing older phases of CBN, a concept supported by intracranial haemorrhage and head trauma groups with a greater extent related to survival despite a terminal therapy in the former and no therapy in the latter.

A last point is that plurifocal and/or interstitial intermyocellular fibrosis may be due to repetitive loss of myocells with collagen substitution secondary to catecholamine myotoxicity with the false impression of a primary collagen matrix proliferation or reparative ischemic fibrosis.

It remains to be established whether the source of catecholamines is blood-borne or intramyocardial in the different pathological conditions. In experimental catecholamine intravenous infusion and in transplanted denervated hearts as well in any similar conditions, e.g. pheochromocytoma, the lesion distribution was similar in both cardiac ventricles. This suggests a blood-borne origin for the damaging catecholamines. In particular, the transplanted heart shows an early depletion of intramyocardial catecholamine with possible up-regulation of β-1 and down-regulation of β-2 adrenoreceptors [51] and supersensitivity to blood-borne catecholamines. In other patterns (Table 3) the adrenergic damage is mainly located in the left ventricle suggesting a prevalent intramyocardial release and reduced uptake of catecholamines via brain stimuli [52], or mechanoreceptor stimulation by local myocardial asynergy [40], or media neuritis at the atherosclerotic plaque level [3, 42] or other still unknown mechanisms. The linkage between adrenergic stress and ventricular fibrillation has already been emphasised. The increasing evidence of a sympathetic denervation in experimental and human coronary and non-coronary conditions [53, 54, 55, 56, 57] suggests that arrhythmogenic sympathetic supersensitivity may depend on a local release of catecholamines by adjacent non-denervated tissue with a possible hyperinnervation [58].

In conclusion we stress that to the best of our knowledge, a comparative study of the frequency and quantitative extent of contraction band necrosis in different conditions was never accomplished previously and that pathological contraction bands are an important histological hallmark of adrenergic stress caused by a variety of mechanisms, intrinsic or extrinsic to the heart. An adrenergic stress is present in various experimental and human conditions with overexpression of β-adrenergic receptors in myocardial fibrosis and congestive heart failure [59] induced by free radicals and prevented by β-blocking [60] and in regional ischemia following angioplastic balloon inflation [61] related to oxidation stress [62].This is a still a relatively unknown field worth investigation to understand malignant arrhythmias and related cardiac arrest. Finally, the relationship between catecholamine peroxidation and contraction band necrosis following calcium reperfusion after calcium-free perfusion ("calcium paradox") remains to be clarified [63].

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