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REVIEW

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Bulbo-spinal pathology in neurocardiac sudden death of adults: a pragmatic approach to a neglected problem

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Abstract This paper gives an overview on the neurocardiopathy of reflexogenic sudden death in adults, focusing on the bulbo-spinal cardiovascular-respiratory centers and which is reminiscent of the recent findings in sudden infant death syndrome. The preeminent life-threatening derangements of the oxygen-conserving cardio-inhibitory reflex (dive-reflex and its subsets) were reconsidered in histopathology, together with bulbo-spinal sympathovagal abnormalities and possible underlying arrhythmogenic QT interval prolongation. A simplified methodology for the microscopical examination of the brain stem and upper thoracic spinal cord is suggested. The aim is to facilitate the pathologist's approach to a lamentably neglected, yet fundamental topic in the far-reaching domain of sudden cardiac death with no evidence of cardiovascular respiratory disease.

Key words Cardiac neuropathology · Neurocardiac sudden death

Introduction

Contrary to the great importance currently attributed by cardiac clinicians and electrophysiologists to autonomic neural derangements in lethal arrhythmias (Randall and Ardell 1990;Randall 1994), the neuropathology of sudden cardiac death(SCD) is lamentably ill-known. This article reunites under the label "neurocardiac" those cases of SCD that do not fall into the nosographic group of classic dysautonomias (Ewing 1989; Goldstein et al. 1997) such as Riley-Day, Shy-Drager and Guillaume-Barré syndromes, Alzheimer's disease or diabetic autonomic neuropathies. It will deal with those cases with abrupt cardiovascular-respiratory disorders which are apparently accounted for by exclusive or preeminent neurovegetative abnormalities and which were not suspected clinically.

The statistical relevance of these is unknown, since they have not yet received adequate attention regarding the pathology of SCD and have not emerged as a body of knowledge in the specialized literature (Rossi and Matturri 1994; Rossi 1995). Oddly enough popular treatises on cardiovascular pathology only hint at neurocardiopathy as being pathognomonic of Chagas' heart disease, whereas this very notion is being disavowed (Rossi 1996). This unfortunate drawback in the basic understanding of SCD is crucial to forensic medicine (Rossi et al. 1991) where professional intervention compulsory by law, is fundamental in judicial settlements as well as in medical assessment of many cases. The main reason seems to be a merely practical one, due to the opinion that the microscopy of cardiovascular autonomic innervation is so difficult as to be accessible only by overspecialized researchers,involved mostly in animal experiments.

Recently, however, studies on the pathophysiology of sudden infant death syndrome (SIDS) have focused on the cardiorespiratory brain stem of infants (Filiano and Kinney 1992; Rossi and Matturri 1995a, 1997) with important results pointing to a reflexogenic lethal mechanism. Similar methods and criteria can well apply to SCD in all age groups, especially in cases which fail to exhibit any clear-cut evidence of potentially lethal cardiovascular-respiratory disease both ante mortem and post mortem.

However, it is well known that SCD is a multifaceted issue (Rossi 1980, 1982, 1985, 1988, 1990, 1992, 1994, 1995; Rossi and Matturri 1985, 1995b) where broad circumstantial and diagnostic criteria are still unsettled and as such can be satisfied by interplaying factors in postmortem epicrisis. Indeed, the commonplace artery disease, whenever manifested with a main functional factor such as the histologically undetectable spasm superimposed upon minor structural changes, is always available to formally overcome pending autoptic doubts. Which also introduces an autonomic neural co-factor, with the awareness that a psychological stress, namely anger-fear,

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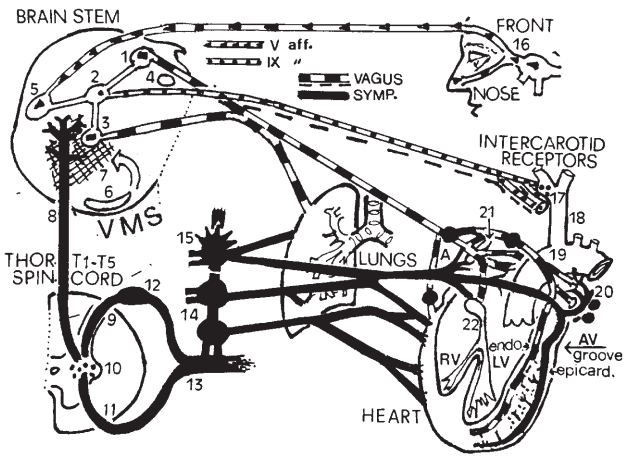

Fig. 1 A scheme of cardiovascular-respiratory autonomic innervation. V aff., IX aff. = trigeminal and glossopharyngeal afferent nerve; SYMP. (and VAGUS afferent/efferent nerves); 2 = nucleus tractus solitarius; 3 = nucleus ambiguus; 4 = nucleus hypoglossus; 5 = trigeminal spinal tract and nucleus; 6 = nucleus arcuatus and ventral medullary surface (VMS) with input(arrow) into 7 = reticular respiratory formation; 8 = spinothalamic tract; 9 = posterior spinal root; 10 = intermediolateral sympathetic neurons; 11 = anterior root; 12 = spinal ganglion (swellings hint at ganglia); 13 = spinal nerve (autonomic and somatic); 14 = sympathetic chain (or trunk) T1-T5 with twin communicating and interganglionic rami; 15 = stellate ganglion; 16 = trigeminal ophthalmic branch from Gasser ganglion; 17 = carotid sinus and intercarotid glomus' receptor; 18 = common carotid artery; 19 = aortic arch; 20 = cardiac plexus (ganglio-paraganglionated) and aorto-pulmonary receptors; 21 = sinoatrial node and ganglionated plexus; 22 = atrioventricular node and Hisian system; AV-groove, below which sympathetic nerves traverse the subepicardium (epic.), while vagal nerves traverse the subendocardium(endo.)

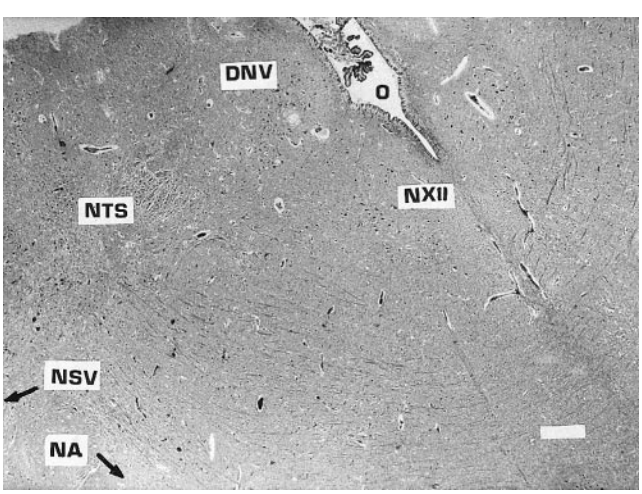

Fig. 2 The brain stem parahypoglossal area in man: at the side of the obex (O), the nucleus hypoglossus (NXII) and the dorsal nucleus of the vagus' (DNV), the nucleus and the tractus solitarius (NTS); close by (beyond the microscopic field) are the spinal trigeminal nucleus (NSV) and the nucleus ambiguus (NA); bar = 0.3 mm

can trigger coronary SCD (Eliot and Buell 1985; Mittleman et al. 1995; Malliani 1996). Such cases will not be taken into consideration here, insofar as the supervening lethal

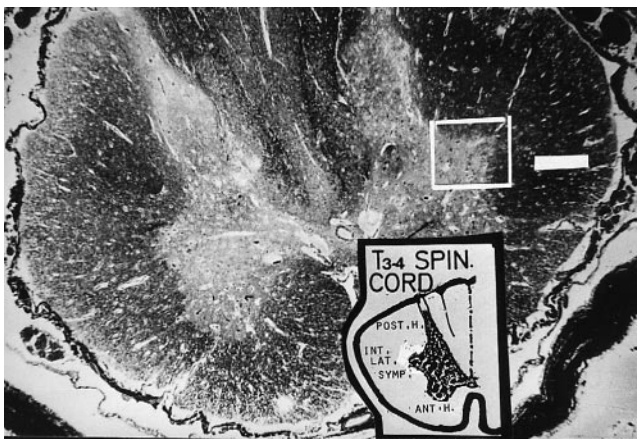

Fig. 3 Thoracic spinal cord (T3-T4) section: the (white-framed) intermediolateral sympathetic center (Bielschowski-stained), and its black-framed schematization; abbreviations. ANT.H = anterior grey horn; INT.LAT.SYMP = intermediolateral sympathetic neuronal column; POST.H = posterior grey horn. Klüver-Barrera; bar = 0.6 mm

changes are cardiac in location and not solely arrhythmogenic in nature from central nervous system abnormalities; the same applies to unexpected death from oligosymptomatic cerebral tumors (Filkins et al. 1996). Altogether this is a pragmatic, synthetic approach to a complex, far-reaching task necessitating oversimplifications and abridgements for the sake of basic information (Figs. 1–3).

The how and why of neurocardiac SCD

Popular wisdom has it that one can die suddenly of sorrow or rage and rare cases of healthy subjects who succumbed to inherent adrenergic arousal are known, but this is not exemplary of neurocardiac SCD. Indeed, psychological forebrain-lymbic stimuli if not entailing swift coronary spasm death, are likely to disorder the heart action by reflex mechanisms, centered within bulbospinal structures in the domain of baro-(mechano)-chemoreflexes (Spyer 1981; Rossi 1992, 1994). These notoriously respond to variations in blood pressure and chemical breathing-dependent components of blood and cerebrospinal fluid (e.g. pO2, pCO2, pH).

The vital/lethal function of these reflexes whose separation in neuroanatomy is unclear (Spyer 1981), plays a major role in the sympathovagal antagonistic balance, which is so dangerously sensitive as to occasionally provoke a cardiovascular-respiratory catastrophe. Like all reflexes they rely on an anatomofunctional arc, set upon twin abutments (Rossi 1992). These are put together by viscerosensitive vago-sympathetic receptors and terminals, converging into afferent nerves that carry the stimuli to the so-called cardiovascular respiratory centers (Figs. 1–3). They are located in the brain stem and thoracic spinal cord (the arc's span) wherein the central neuronal circuits coordinate and modulate the reflexogenic input with the interplay of upper and lower extra-bulbar stimuli

(Rossi 1994). Thereafter these are sent back (often via the same nerves and plexuses) as efferent impulses to the visceromotor terminals so activating the reflex response. The baro-chemoreflex response is mainly inhibitory-parasympathetic (Levy 1977; Cardinal 1994) slowing heart beat, lowering blood pressure and/or disordering respiration, which explains why the present synoptic outlook focuses on the central keystone of the arc. However, it is self-explanatory that any derangement of the antagonistic vago-sympathetic balance is liable to bring about unpredictable responses, not shown in the scheme.

Bulbo-spinal background for reflexogenic SCD

The examination will be confined to the following crucial structures (Rossi 1994; Kahle 1991, Figs. 1–8): nucleus and tractus solitarius (vagal and glossopharyngeal-mainly afferent), nucleus ambiguus (vagal afferent-efferent, glossopharyngeal afferent), dorsal nucleus of the vagus' (visceromotor/efferent), nucleus arcuatus, ventral medullary surface (chemosensitive), linked with ventrolateral respiratory reticular formation (Filiano and Kinney 1992), trigeminal spinal tract and nucleus (fronto-nasal mucocutaneous sensory afference) relayed to the cardiovascular neuronal circuitry, thoracic spinal cord T1-T5 grey (sympathetic neurons) and ascending spino-bulbar-thalamic tract (Foreman 1994) (Figs. 1 and 6).

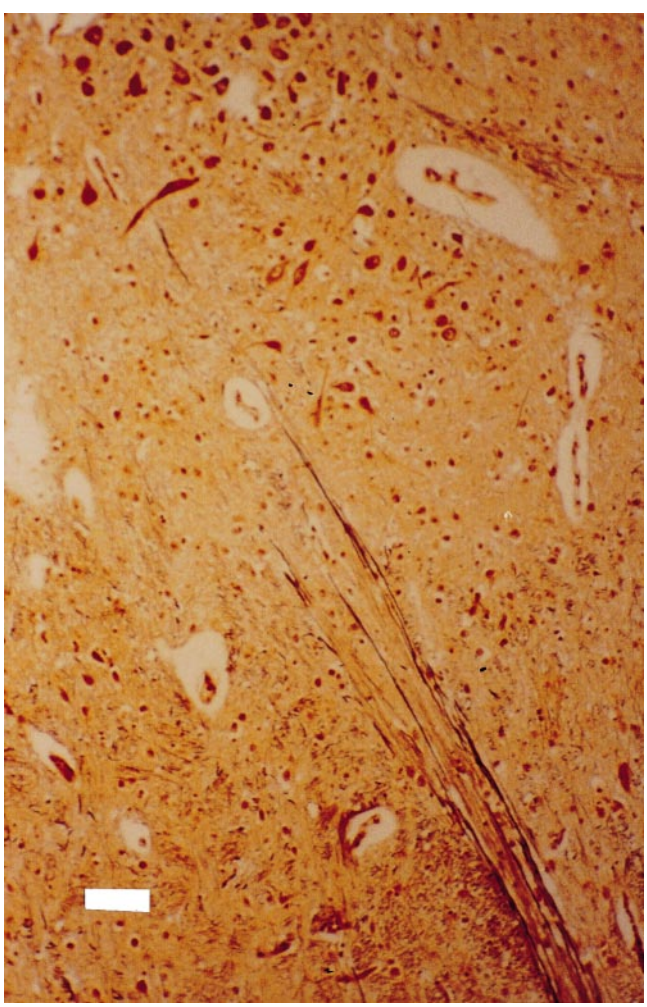

Fig. 4 The keystone of the inhibitory cardiovascular reflexogenic arc in man: the dorsal vagus' nucleus (above) and the nerve root (below). Bielschowski; bar = 40 μm

Clinicopathological setting of reflexogenic SCD

Cardiovascular-respiratory reflexes in humans are not fully understood because they are not clearly comparable with those in animal experiments. In neurocardiac sudden death, the reflexogenic mechanism can be broadly regrouped into the domain of the dive (oxygen-conserving)-reflex (Wolf 1978; Rossi 1992, 1996). As subsets, Ondine's curse and death feigning or fear paralysis can be taken into consideration which share some nerve pathways and centers (Folgering et al. 1979; Kaada 1995). These reflexes are also likely to play an important role in SIDS, as well as to interplay in so-called voluntary sudden death occurring from the West Indies to the Far East (Myerburg 1978), countersigned by an arrhythmogenic marker (Nademanee et al. 1997).

It is interesting to note that the dive reflex and it's subsets are regarded as phylogenic relics, paradoxically re-emerging in humans. Indeed the oxygen-conserving dive reflex is particularly developed in flying birds (Rossi 1990) to secure inhibition of cardiac and breathing rate during underwater feeding, necessary for individual and species survival. The same may apply to Ondine's curse reflex, where the denomination recalls water immersion and is based on a Giraudoux comedy wherein a siren witch compels her human lover to breathe only by volition; an aberrancy clinically transposed to sleep apnoea syndrome and SIDS (Folgering et al. 1979). Likewise the death feigning-fear paralysis reflex (Thach et al. 1988; Kaada 1995) is thought to reproduce an instinctive suppression of bodily movements with drastic reduction of cardiac and respiratory rates, exhibited by wild mammalian cubs when menaced by carnivorous predators (known not to prey on carrion), which is also relevant to SIDS and/or to the quoted psychogenic SCD in adults. Fear paralysis can be related also with cardioauditory death, e.g. SIDS from sudden loud noises, long QT syndrome (Guntheroth 1995; Schwartz et al. 1991a,b). The reflex arc is a complex one, spanning from the temporal cortex to the spinal sympathetic intermediolateral horn via mesencephalic pathways (the lateral lemniscus is accessible to routine study). Even more complex is the Bezold-Jarisch reflex (Mark 1983) still uncertainly labelled as a baro- or chemoreflex with sympathovagal derangements (arrhythmias, hypertension, hypo- or hyperventilation). Although important, this will not be discussed to avoid straying into pathophysiological debates.

The quoted reflexogenic aberrances are peculiar to SIDS but can possibly reveal themselves in adult life, whether or not combined with acquired bulbo-spinal dis-

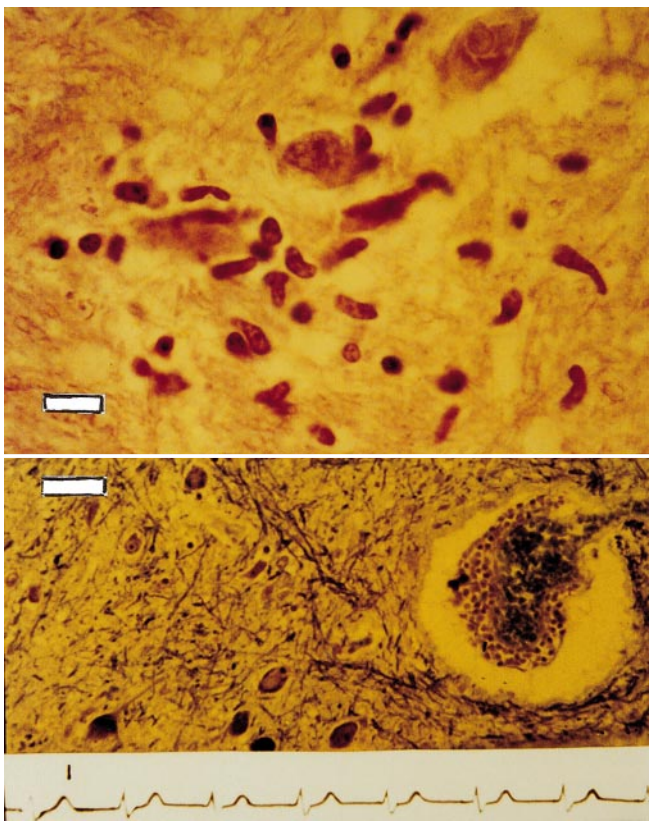

Fig. 5 Above: gliosis with neuronal degeneration and (below) encephalitic perivasculitis of the vagus' dorsal nucleus in a case of SCD heralded by sinus arrest with accelerated junctional escape rhythm (electrocardiogram at bottom). Above: Hematoxylin-eosin; bar = 20 μm; below: Klüver-Barrera; bar = 40 μm

ease likely to strongly enhance the arousal, or to depress and retard the withdrawal of cardio-respiratory inhibition, theleologically directed to preserve life in lower animals, yet becoming highly risky in humans.

The hypothesis can be put forward that the enormously preeminent evolution of the human forebrain (telencephalization, Rossi 1990) if compared with lower phylogenic groups has so enriched the reflex psychological conditioning as to make these reflexogenic relics paradoxally lethal to man. Which can be exemplified in SCD from the dive reflex of subjects who underwent sinus arrest only by thinking of and/or preparing to dive (Wolf 1978).

In turn, lethal tachyarrhythmia can supervene by psychogenic adrenergic hyperstimulation entailing repolarization derangements with long QT interval (Topaz et al. 1988; Schwartz et al. 1991a,b). Familiar cases, recently attributed to threefold genetic abnormalities (Rosen 1995) are yet subject to acquired hypersympathetic triggering of torsade de pointes (Schwartz et al. 1991a). Findings in one of the present cases (Fig. 6) seem to be consistent with this hypothesis.

Bulbo-spinal pathology in SCD

Leaving aside the findings in SIDS, the author will summarize some personal cases where central neurocardiac changes plausibly accounted for SCD, insofar as no cardiocirculatory-respiratory damage was found (conduction system and intrinsic heart innervation included). Therefore, although not drawing definite clinicopathological correlates, it is suggested that a neurocardiac examination should be carried out in any similar case which lamentably would be lost in routine post-mortem controls (Rossi et al. 1991).

Pathology features of viral encephalitis (virus unidentified) with focal perivascular round-cell infiltration and sparse gliosis were observed in two cases (Alampi et al. 1990; Rossi 1994) with gastro-esophageal (in one) and profuse sialorrhea (in both) from vagal hyperexcitation, who died suddenly from cardiac arrest, preceded by intermittent sinus arrest with junctional escape and/or tachyarrhythmias. In both cases inflammatory and degenerative changes of the brain stem involved the nucleus ambiguus, and the dorsal nucleus of the vagus' (Fig. 5). Likewise four cases of SIDS (lacking clinical data) exhibited histopathology changes similar in location and type (Rossi and Matturri 1995b). It should be pointed out that in all of the cases the structural abnormalities were located inside, or close to the ventrolateral reticular formation implying associated respiratory derangements. The importance of breathing abnormalities in brain stem pathology of sudden death was recently emphasized in SIDS, particularly in a recently published case with focal T-lymphocytic inflammation of the ventral medullary surface and subjacent nucleus arcuatus (Rossi and Matturri 1997, Fig. 9).

SCD, heralded by highly arrhythmogenic derangements of repolarization (long QT interval) could be attributed to hitherto undescribed central nervous system changes. Indeed, in two cases of Creutzfeldt-Jakob disease encephalopathy, spongiform involvement of the dorsal vagus nucleus and Kuru plaques in the nucleus ambiguus and tractus solitarius were observed (Valli et al. 1994). Likewise, in one case, thoracic spinal cord (T3-T4) radiculitis-pachymeningitis and severe tigrolysis of the sympathetic intermediolateral neurons (Fig. 6) could have accounted for tachycardia and QT interval prolongation (Karjalainen et al. 1994; Rossi and Matturri 1995b).

Of great importance in SCD are all changes of the afferent peripheral and of brain stem neuronal circuitry centered on the nucleus and tractus solitarius (Fig. 1) of the glossopharyngeal nerve (Cicogna et al. 1990). Reflexogenic disorders can lead to lethal inhibitory action on the sinoatrial node, with sinus escape and possible sudden cardiac arrest. This is confirmed by adult cases of SCD with attacks of glossopharyngeal neuralgya (Sobel et al. 1981) and/or in the glossopharyngeal space syndrome (Cicogna et al. 1993). Accordingly, in a case of SIDS (Rossi and Matturri 1995a) the single pathology finding was a focal degeneration (demyelination and neuronal loss) of the tractus and nucleus solitarius.

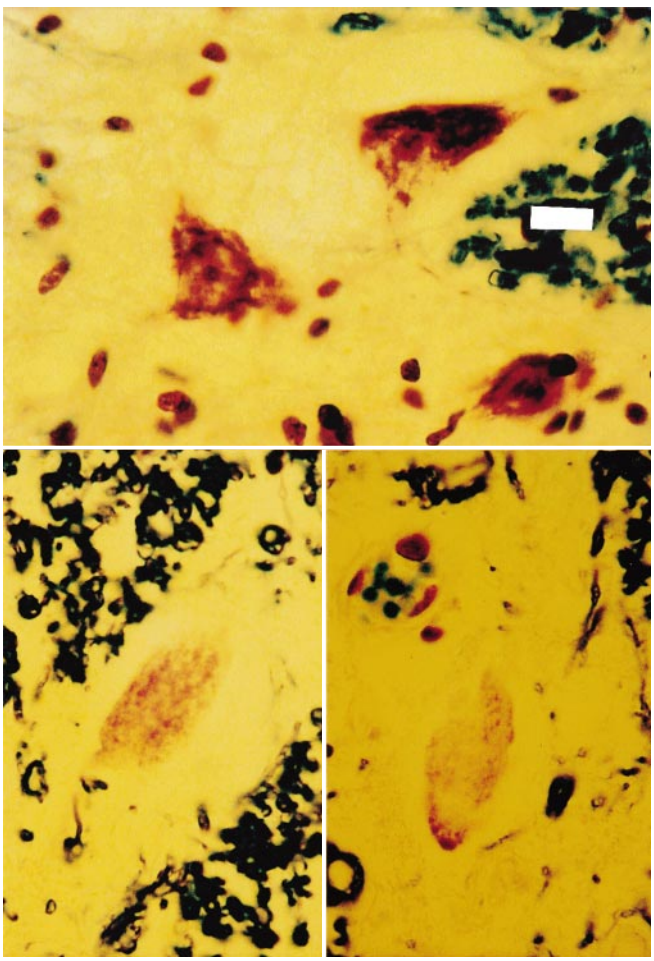

Fig. 6 Neurons of the sympathetic cardiovascular-respiratory center (spinal cord T3-T4): normal control (above), and severe tigrolysis (below) in a case of arrhythmogenic SCD, heralded by tachycardia and prolonged QT interval. Klüver-Barrera; bar = 20 μm

These observations also make one wonder whether subjects who die suddenly while swimming or diving, currently believed to have drowned after a digestive malaise, might have been victims of a derangement of the dive reflex and/or its subsets. Also typical is a case of lethal cardiac arrest in a young army recruit (unpublished) who succumbed to the common barracks-prank of pouring a mess-tin of cold water on the face of a sleeping comrade. Abrupt vagal hyperexcitation from an aberrant dive reflex due to trigeminal-ophtalmic triggering was the most plausible explanation, but no aimed control of the central nervous system was carried out.

To these examples of SCD neuropathology, the author adds a hint at medico-legal implications of inherent histopathological evidence in a case tried in court, perhaps the first one officially recorded (Rossi 1995). It concerns the trial of a hockey player prosecuted in Italy for voluntary manslaughter of an opponent to whom he had inflicted a stick-slash on the thorax (padded) that apparently caused SCD (Swift 1993). No traumatic lesions were detected postmortem while the heart was declared normal without any microscopy control of the conduction system or of the innervation. The striker (an american boy) risked a 10-years jail sentence for killing a perfectly healthy athlete. The defense summoned this author to reexamine the seriously defective histological documentation, the rest having been uncautiously thrown away. Focal atrial epicarditis of the upper crista terminalis was detected (close to the lost sinoatrial node), together with a diffuse degeneration of intrinsic ganglia with growing satellitosic Terplan nodules (Rossi 1996) very rare in the young, altogether potentially arrhythmogenic in nature. The judge sentenced that the victim was a sick man at risk who, as such, should never had been allowed to engage in competitive violent sports. The indictment was downgraded and the defendant was fined and acquitted. Neuropathology has entered among the officially accepted causes of SCD.

A practical method to approach the neuropathology of SCD

A preliminary consultation of an authoritative, concise textbook of neuroanatomy and physiology (Kahle 1991) is advised to allow a better grasp of the present outline of bulbo-spinal neuropathology of SCD. It is however self-evident that when dealing with structures organized in a reflex arc, the pathological control should be as comprehensive as possible. In practice, however, it would be impossible and enormously time consuming to control myriads of widespread nerve plexuses and visceral terminals of the cardiovascular-respiratory periphery, while the examination of the bulbo-spinal centers can secure more rapid and relatively more reliable results. Even the finding of minute neuropathological features in central neuronal circuitries can underlie more severe reflex derangements, when compared with discrete abnormalities in the widespread autonomic periphery. This applies particularly to encephalitic focuses, often detected in the brain stem of victims of neurocardiac sudden death, in infants and also in adults.

To excise the most suitable block of the brain stem (Fig. 8), one should look at the caudal part of the floor of the 4th ventricle and cut transversal (or slightly oblique dorso-ventral) sections about 3 mm above and 1 cm below the obex. The tissue block, fixed in buffered formalin and embedded in paraffin should be sectioned in series at 100–200 μm intervals (beginning from the upper surface). The sections, glued with a protein-free adhesive to the glass, should be stained routinely with hematoxylin-eosin (HE) and with Klüver-Barrera (myelination, neuronal tigroid substance: Okazaki 1989) and Ag impregnation (Bielschowski, or analogue; monoclonal antibodies if necessary); other special methods are optional.

The thoracic spinal cord should be cut transversally (Fig. 3) between T1 and T5. Despite the gross difficulty in manipulation (chiselling out the bone around the vertebral foramina) it would be desirable to ablate, contemporarily (especially on the left side) the spinal nerve roots and gan-

glia. The histological treatment is the same as that for the brain stem.

"Pathfinder" histological overview of the brain stem

A straightforward procedure throughout the bulbospinal neuronal circuitries: under the microscope, and keeping the floor of the 4th ventricle upwards (Fig. 2), at either side of the obex one easily recognizes the subependimal large neurons of the nucleus hypoglossus (Fig. 2) and, laterally beyond the tiny nucleus intercalatus, the all-important dorsal nucleus of the vagus' and its nerve root are often visible (Fig. 4). More laterally (and slightly lower-ventral), a nerve-like bundle of fibers (cut transversally) with neurons all around consist of the tractus and nucleus solitarius (Fig. 8). Even more laterally (and lower-ventral) a similar but larger nerve-like structure and grouped neurons which form together the trigeminal spinal tract and nucleus (Fig. 8). Below (ventral) there is the large fes-

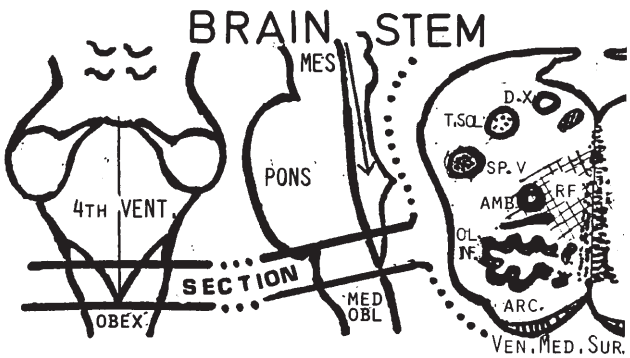

Fig. 8 The "pathfinder" overview (different levels) of a schematized cardiovascular-respiratory neuronal circuitry of the brain stem, and of its macroscopic ablation, abbreviations: AMB = nucleus ambiguus; ARC = nucleus arcuatus; DX = dorsal nucleus vagus; MED.OBL. = medulla oblongata, MES = mesencephalon; OL.INF. = oliva inferior; RF = reticular formation; SPV = spinal nucleus trigeminal; T. = tractus and nucleus solitarius; 4th VENT = fourth ventricle; VEN.MED.SUR.: ventral medullary surface

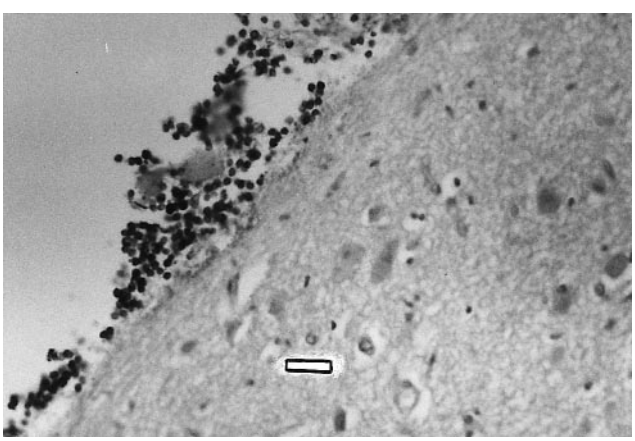

Fig. 9 T-lymphocytic leptomeningitis of the chemosensitive ventral medullary surface overlying the nucleus arcuatus, in a case of SIDS. Immunohistochem.; bar = 30 μm

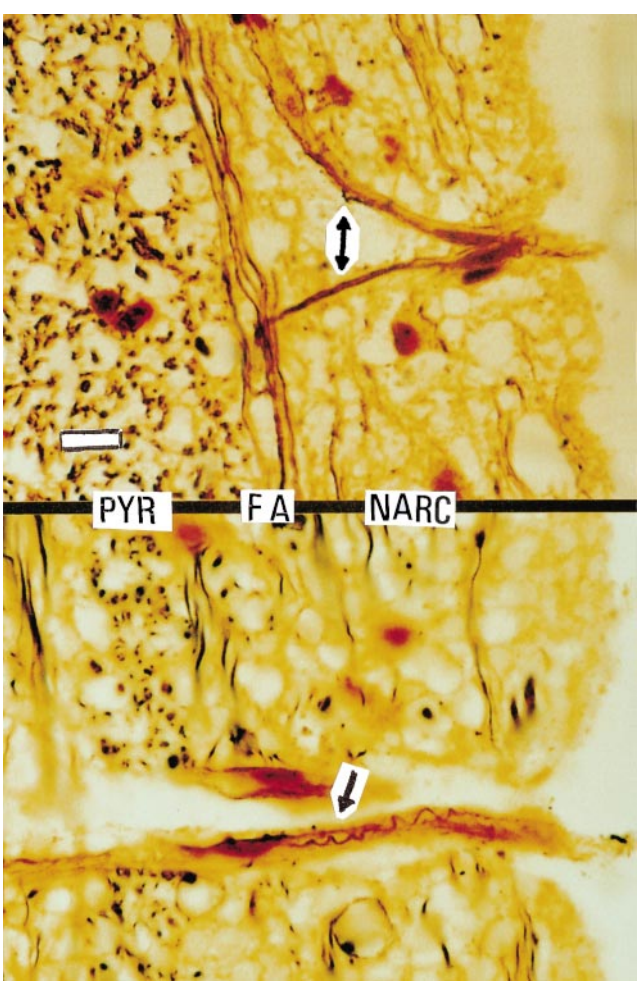

Fig. 7 Ventral medullary surface: apparent chemosensitive nerve terminals of fibrae arcuatae externae (FA) accompanying large capillaries (arrows), abutting on the subarachnoid space, at the periphery of the nucleus arcuatus (ARC) and the pyramid (PYR). Bielschowski; bar = 20 μm

tooned nucleus olivaris inferior (Fig. 8) where the posterior (higher) portion is close to a small collection of very large neurons, pertaining to the uppermost nucleus ambiguus, encompassed by the respiratory reticular formation. Some authors refer to a magnocellular nucleus of the reticular formation, to the risk of semantic confusions (Kinney et al. 1995). The same may apply to the denomination (in animal experiments) of the Bötzinger complex (Hopkins and Ellenberg 1994) of the nucleus ambiguus, intimately involved in respiratory regulation.

Below and beyond the pyramidal bundle, special attention will be dedicated to the nucleus arcuatus, squeezed at the subarachnoidal surface of pyramid periphery. This is occasionally subdivided into more or less developed arborisations, whose size is relevant to SIDS (Filiano and Kinney 1992) and sends axons upwards to the reticular formation and to the cerebellum.

The emphasis now laid on the respiratory reflexogenic function of the chemosensitive ventral medullary surface (Fig. 9) especially in SIDS (Filiano and Kinney 1992;

Rossi and Matturri 1997), is hitherto lacking a precise histological peculiarity. New evidence is shown here of large capillaries with nerve endings, abutting from the fibrae arcuatae externae and surfacing on the ventral medullary subarachnoid space (Fig. 7), morphologically consistent with a chemoreceptor function. This hypothesis can be related also with the topographic vicinity of the area postrema, critical to blood-spinal fluid exchange (Bonhann and Wilson 1995).

Regarding the spinal cord (Figs. 3, 6), the recognition of sympathetic neurons in the T1-T5 intermediolateral horn is easy.

To go on with the examination of the afferent-efferent abutments of the cardiovascular baro-chemoreflex arc, the following structures would be ablated: intercarotid receptors (glomus and sinus), mediastinal extrinsic cardiac plexus, with inherent ganglia and paraganglia, aortic arch nerve terminals, left stellate ganglion (Rossi 1990, 1995; Rossi and Matturri 1995b).

Final remarks

The data and arguments presented provide a synoptic survey to open, rather than to conclude, a far-reaching subject as an invitation to motivated pathologists to participate in obsolete forms of research. The pragmatic abridgements detract from completeness, but would at least make it easier to preserve interesting material for further, finer investigations by specialists. Thereby, more coordinated and consistent documentation than hitherto available, will widen and update the pathological assessment of SCD.

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