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Vibroacoustic disease

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Abstract

Vibroacoustic disease (VAD) is a whole-body, systemic pathology, characterized by the abnormal proliferation of extra-cellular matrices, and caused by excessive exposure to low frequency noise (LFN). VAD has been observed in LFN-exposed professionals, such as, aircraft technicians, commercial and military pilots and cabin crewmembers, ship machinists, restaurant workers, and disk-jockeys. VAD has also been observed in several populations exposed to environmental LFN. This report summarizes what is known to date on VAD, LFNinduced pathology, and related issues. In 1987, the first autopsy of a deceased VAD patient was performed. The extent of LFNinduced damage was overwhelming, and the information obtained is, still today, guiding many of the associated and ongoing research projects. In 1992, LFN-exposed animal models began to be studied in order to gain a deeper knowledge of how tissues respond to this acoustic stressor. In both human and animal models, LFN exposure causes thickening of cardiovascular structures. Indeed, pericardial thickening with no inflammatory process, and in the absence of diastolic dysfunction, is the hallmark of VAD. Depressions, increased irritability and aggressiveness, a tendency for isolation, and decreased cognitive skills are all part of the clinical picture of VAD. LFN is a demonstrated genotoxic agent, inducing an increased frequency of sister chromatid exchanges in both human and animal models. The occurrence of malignancies among LFN-exposed humans, and of metaplastic and displastic appearances in LFN-exposed animals, clearly corroborates the mutagenic outcome of LFN exposure. The inadequacy of currently established legislation regarding noise assessments is a powerful hindrance to scientific advancement. VAD can never be fully recognized as an occupational and environmental pathology unless the agent of disease - LFN - is acknowledged and properly evaluated. The worldwide suffering of LFN-exposed individuals is staggering and it is unethical to maintain this status quo.

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Full Text

Introduction

For the past two millennia, acoustic events have been associated with hearing impairment. Within the past 200 years, human civilization has been an ever-increasing source of acoustic energy, on par only with the amount of light that is produced on our planet. However, unlike electromagnetic radiation, where different frequencies are known to produce different health hazards, with acoustic energy no such information is available. Despite the substantial body of evidence indicating that acoustic phenomena impinges on more than just the ear, "noise" continues to be assessed based on the assumption that only what the individual hears is harmful (Alves-Pereira and Castelo Branco, 1999). The implication that an agent of disease has to be perceived to be harmful is ludicrous: xrays, for example, are not perceived by humans, but are, nevertheless, a fully recognized health hazard.

In 1928, Laird published one of the first studies on the physiological effects of noise on typists (Laird, 1928), and since then, vast amounts of medical and biomedical studies have appeared in the literature (Alves-Pereira, 1999). In 1946, E. Dart, employed as a physician at the Ford aircraft engine manufacturing plant, in Detroit, MI, USA, described a set of symptoms observed in aircraft technicians (Dart, 1946). Rumancev, in 1961, describes the same collection of symptoms that he observed in a population of workers employed by a reinforced concrete factory, in the Soviet Union (Rumancev, 1961). Cohen, in the USA in 1971, reported on the medical complaints of boiler-plant workers, before and after the implementation of a hearing conservation program, and listed similar symptoms as Dart and Rumancev before him (Cohen, 1971). Grechkovskaia et al. speak of a "vibronoise pathology" in workers employed at an aircraft industry in Kiev, Ukraine (Grechkovskaia et al. 1997). Balunov et al. studied workers engaged in ferro-concrete production in St. Petersburg, Russia, under combined vibration, infrasound and noise, and concluded that this group had an increased morbidity (Balunov et al., 1998). In 86 female textile workers, Magomedov et al. identified disturbances of the autonomic and central nervous systems that preceded hypoacousis, such as asthenovegetative and neurotic syndromes (Magomedov et al, 1997). Also in 1997, Izmerov et al. suggested the existence of a whole body response to infrasound (Izmerov et al., 1997).

In 1979, the health of workers employed by the Portuguese Air Force, at an aircraft maintenance, repair and manufacturing plant (OGMA), was placed under the care of author Castelo Branco. While visiting all work-stations, he witnessed an aircraft run-up procedure and observed a technician walking about aimlessly, in what appeared to be an epileptic-like episode (Castelo Branco and Rodriguez, 1999). This prompted an investigation into the medical records of all aircraft technicians to determine how many had been previously diagnosed with late-onset epilepsy. The astounding number of 10%, versus the expected 0.2% found among the Portuguese population, was the basis for the in-depth neurological evaluation that ensued (Castelo Branco and Rodriguez, 1999).

Until 1987, aircraft technicians employed by OGMA received a series of medical tests that included brainstem auditory evoked potentials, brain MRI, cognitive tests and neurological examinations. All subjects were fully-informed volunteers. A large amount of neurological changes were identified in this group of aircraft technicians (Martinho Pimenta and Castelo Branco, 1999a) that included brain lesions and increased latencies in nerve conduction (Pimenta et al., 1999), decreased cognition (Gomes et al., 1999) and the appearance of archaic reflexes (Martinho Pimenta et al., 1999a).

The First Autopsy

In 1983, the first patient in this group died suddenly, and an autopsy was not possible. This irritated Mr. Felipe Pedro, another aircraft technician, who had taken an academic interest in his health problems. The event prompted him to draw up a legal will, demanding that, upon his death, an autopsy be performed by Castelo Branco. Mr. Felipe Pedro worked as a ship machinist in the Portuguese Navy for 10 years prior to being hired by OGMA, in 1959, as an aircraft technician. A detailed description of the course of his medical evolution is given elsewhere (Castelo Branco, 1999a).

One early September morning in 1987, Castelo Branco received a phone call from Mr. Felipe Pedro who told him that he was very ill and was going to die. He asked Castelo Branco to meet him at the hospital so the autopsy could be performed. When Castelo Branco reached the hospital, Mr. Felipe Pedro was deceased. And the autopsy was performed. The findings so graciously provided to us by Mr. Felipe Pedro have been the basis for much of the subsequent research into noise-exposed workers.

Diagnosed with late-onset epilepsy in 1981, this man died at age of 58, of cardiac tamponade caused by a small

infarct. His heart disclosed 11 small scars of previous silent ischemic events. Cardiac valves seemed swollen, and the pericardium surrounding the heart was greatly thickened. Coronary arteries were thickened, but not by the usual, and expected, artherosclerotic plaques. Instead, a continuous thickening of the intima lined all vessel walls. Microscopic studies later revealed that much of the thickening was due to abnormal proliferation of collagen fibres. Two tumours were found, a Grawitz in the kidney, and a grade I, microcystic astrocytoma in the right parietal region of the brain.

Echocardiography

The autopsy findings of thickened cardiac structures led to the echocardiographic study of the population of aircraft technicians. All had thickened pericardia, and many also exhibited thickened cardiac valves (Marciniak et al., 1999). A literature review revealed that Prof. Matoba, in Japan, had already identified pericardial thickening in some chainsaw workers (Matoba, 1983). Today, pericardial thickening in the absence of an inflammatory process, and with no diastolic dysfunction, is the hallmark of VAD (Holt, 2000). Pericardial thickening among LFN-exposed individuals has been anatomically confirmed through light and electron microscopy studies of VAD patient pericardial fragments (collected with patients' informed consent, during cardiac bypass surgery received for other reasons) (Castelo Branco et al., 1999a, 2001, 2003a,b).

Echo-imaging equipment for cardiac structures has many manufacturers and many different models. Enhancing the view of pericardial thickening is not an established procedure. Thus, technician-dependent subjectivity is still inherent to this diagnostic method for VAD. Nevertheless, echocardiography is still the standard test for diagnosing VAD. Thickened cardiac structures have been observed in aircraft technicians (Marciniak et al., 1999), commercial airline pilots and flight attendants (Araujo et al., 2001), and in an islander population exposed to environmental LFN (Torres et al., 2001). Thickening of cardiovascular structures has also been observed in LFN-exposed animal models (Castelo Branco et al., 2003c).

The Clinical Stages of Vibroacoustic Disease

The evolution of VAD, as per years of occupational exposure, was defined in 1999 (see [Table 1]) (Castelo Branco,1999b). Establishing the evolution of VAD was not an easy task given the insidious nature of this pathology. In an initial group of 306 male aircraft technicians, all employed by OGMA for more than 10 years, rigorous selection criteria were applied as per [Table 2]. A group of 140 technicians (average age of 42 years, SD=10.4) remained after the application of selection criteria, i.e., 166 individuals were excluded.

OGMA, founded in 1918, possessed an on-site medical unit where all employees were seen when hired, and an individual medical file was opened. Subsequently, all annual examinations and medical complaints were recorded in the employee's medical file. The on-site medical unit offered employees a variety of medical specialties free of charge, such as internal medicine, cardiology, endocrinology, psychiatry, neurology, clinical and social psychology, dentistry, orthopaedics, general surgery, ophthalmology and otorhinolaryngology. An employee who required a specialist not available in the on-site medical unit, and wanted to make use of the National Health Care System, had to be referred to that specialist by one of the on-site general physicians. All medical information was thus recorded in all employee medical files.

The medical files of the 140 technicians were comprehensively and chronologically reviewed. Simultaneously, a sociologist and a social worker interviewed family and friends to obtain additional information on the individual's behaviour outside his professional activity. The methodology to obtain a correspondence between sign/symptom and years of occupational exposure was the 50% cut-off, i.e., the sign/symptom was included in the list if it was identified in 50% (N=70) of the study population. Thus, referring to [Table 1], after 1-4 years of occupational exposure, at least 70 of these 140 individuals developed bronchitis, in smokers and non-smokers alike (smokers in study group: N=45). Or, after 10 years of occupational activity, at least 70 exhibited headaches and nose bleeds. It should be emphasized that these signs and symptoms are not mutually exclusive, and most VAD patients suffer from more than one or two of these clinical situations, simultaneously (Castelo Branco, 1999b).

[Table 1] refers to the signs and symptoms developed specifically by aircraft technicians working the standard 8 hrs/day, 5 days/week. Not all LFN-exposed workers have this exposure schedule. For example, ship machinists can spend 3 weeks onboard ship (i.e., exposed to substantial LFN-rich environments) and 2 weeks at home (i.e., presumably not in LFN-rich environments) (Arnot, 2003). Other professional activities exist where the LFN-exposure time pattern is not the standard 8-hr/day exposure, such as with submarine and oil rig operators, and astronauts. In these cases, the evolution of signs and symptoms could be greatly accelerated. Moreover, since different LFN environments have unique frequency distributions, the fact that some frequency bands may be more predominant than others (i.e., concentrate more acoustical energy) can lead to the development of slightly different pathology. If the LFN exposure is environmental and/or leisurely, the standard 8hr/day model is also not applicable.

Associated Pathology

Other important pathologies were identified among these 140 aircraft technicians, but since they were not identified in 50% of the population, they were not included in [Table 1]. Nevertheless, their incidence is clinically important.

Some kind of respiratory insufficiency was found in 24 of the 140 professionals, 11 were smokers. In 10 of the 24 cases, a mere light physical effort was necessary to produce symptoms. Notably, only 45 of the 140 individuals were smokers, 38 of which had over 20 years of occupational LFN exposure.

Late-onset epilepsy was diagnosed in 22 individuals, some of whom saw their seizures subside when away from their workstation. Reflex epilepsy due to vibratory stimulus (Martinho Pimenta and Castelo Branco, 1999b) and visual stimulus was observed in two individuals. Auditory stimuli did not trigger seizures but, in some cases, triggered rage reactions and movement disorders (Martinho Pimenta and Castelo Branco, 1999c).

Balance disturbances were also a common complaint, identified in 80 individuals, although the severity of the balance disturbance ranged from dizziness to severe vertigo (Martinho Pimenta et al., 1999b). Unique and sudden episodes of non-convulsive neurological deficit occurred in 11 individuals. These were diagnosed as cerebral ischemic vascular accidents, which was compatible with imaging studies. EEG and multi-modal evoked potentials showed considerable power changes that were in agreement with clinical psychological and neurological evidences. Delays in multi-modal evoked potentials (including endogenous), observed in all 140 patients, are a sign of progressive neurological deterioration and early aging process, as is the appearance of the archaic palmo-mental reflex, that affects about 40% of these 140 patients.

Other important pathologies observed among these 140 individuals were endocrine disorders, the most common being thyroid dysfunction (18 cases). The overall national Portuguese rate for adult thyroid dysfunction is 0.97% vs. the 12.8% identified in our group of 140 technicians. Similarly, diabetes was seen in 16 individuals (average age 39 years, SD=7.8) (11.4%), while the overall national rate for a similar age-group is 4.6% (Castelo Branco, 1999b).

Among the 140 professionals, 28 had malignant tumours. Five of these 28 individuals exhibited simultaneous tumours of different types. All CNS tumours (N=5) were malignant gliomata, and all respiratory system tumours were squamous cell carcinomas (5 in lung, 1 in larynx). Other tumours were found in the stomach (N=10), colon and rectum (N=9), soft tissue (N=1), and bladder (N=1) (Castelo Branco, 1999b). All digestive system tumours were low-differentiated adenocarcinomas. These data led to the investigation of the genotoxicity of LFN. In both human (Silva et al., 1999 a,b) and animal (Silva et al., 2002) models, LFN induced an increased frequency of sister chromatid exchanges, effectively demonstrating that LFN is a genotoxic agent.

More recently, in 2003, a new pathological sign was identified among VAD patients: decreased respiratory drive (Reis Ferreira et al., 2003a; Castelo Branco et al., 2003d). To date, pulmonary function tests are normal in VAD patients, with the singular exception of the P 0.1 (CO_2) index, which is a measure of the inspiratory pressure (or suction) developed at the mouth, 0.1 seconds after the start of inspiration. This initial respiratory drive originates in the autonomic (or involuntary) pathway of the neural control of the respiratory function. By rebreathing CO_2, normal individuals would present a minimum six-fold increase of the P 0.1 (CO_2) index when compared to normal P 0.1 .If the neural control of respiration is compromised, then a less-than six-fold increase would be expected in the P 0.1 (CO_2) index (Calverly, 1999; Cotes, 1993; Gibson, 1996). In VAD patients, all P 0.1 (CO_2) index values are below 50%,

when normal values would be above 60%.

Lastly, the issue of auto-immune diseases in LFN-exposed individuals. In the electron microscopy studies of VAD-patient pericardial fragments, non-apoptotic cellular death was frequently observed (Castelo Branco et al., 2003a). Instead, biomechanical forces seemed to be responsible for the images of burst cells, with live organelles and no surrounding plasma membrane. Under these circumstances, the appearance of auto-immune diseases in these patients is not unreasonable. Indeed, previous studies have shown that LFN exposure induces an accelerated onset of lupus in lupus-prone mice (Aguas et al., 1999a). Lupus has also been identified in flight attendants (Araujo et al., 2001), and in entire families of islanders exposed to environmental LFN (Torres et al., 2001). Vitiligo is another common finding, especially in the LFN-exposed islander population. Vitiligo is associated with immune changes of CD8 and CD4 lymphocyte populations. These immune changes have also been observed in LFNexposed workers (Castro et al., 1999) and animal models (Aguas et al., 1999b). Other authors have also corroborated the existence of auto-immune processes in noise-exposed workers (Matsumoto et al., 1992, 1989; Jones et al., 1976; Soutar et al., 1974; Lippmann et al., 1973).

Control Populations

One of the most difficult tasks of conducting studies related to LFN-induced pathology is the lack of viable control populations. By definition, in LFN-related studies, control populations are individuals who are not exposed to LFN.

However, given the ubiquitous nature of LFN, control populations are not easy to find. Since the inadequate selection of control populations has given rise to conflicting results (ASTDR, 2001), it is pertinent to tackle this issue head on.

LFN is not legislated, and is therefore allowed to proliferate in almost every sector of human society. LFN exposure is not an exclusive feature of blue-collar workers. In fact, LFN exposure is an integral part of many leisurely activities and of many public transportation settings. [Figure 1],[Figure 2],[Figure 3],[Figure 4],[Figure 5] and [Table 3], compare the LFN levels of the cockpit of the Airbus-340 (Alves-Pereira et al., 2001) with several locations commonly used by the public at large. Even the common passenger vehicle is a significant source of LFN (See [Figure 5] and [Table 3]). So what is the profile of an adequate control population? Consider the following: control populations in any study are not usually monitored in terms of previous LFN exposure; thus, any control population of any study can be skewed because of the existence of a confounding factor - LFN. Moreover, considering the whole-body effects of excessive LFN exposure, compromising the cardiorespiratory and autonomic nervous systems, the degree of error may be significant.

In the specific cases where the investigation focuses on LFN exposed individuals in a certain industrial plant (for example), a control population selected merely on the criterion that they do not work at the industrial plant under study is invalid, because LFN exposure exists in many locations of our everyday life (See [Figure 1],[Figure 2],[Figure 3], [Figure 4],[Figure 5]). The most blatant example of inadequate selection of control populations is the Vieques Heart Study (ASTDR, 2001). Here, individuals who resided in an LFN-rich island (LFN produced by military training exercises) were compared to individuals who lived on another island. Living on another island and agematching were the sole criteria for the selection of the control population in this study. This assumes that no LFN exposure exists on the other island, which is, of course, absurd, and is evidenced in the published results (ASTDR, 2001). Given what is known to date, control populations for LFN studies must be selected on the basis of negative VAD-related tests, (i.e., no pericardial nor cardiac valve thickening, and normal $P0.1(CO_2)$ index), or must otherwise be considered non-controls.

Lastly, animal models also require control populations, and animal studies rarely monitor their acoustic environments. Hence, animal studies may also incorporate a significant confounding factor - LFN. The situation is further aggravated by the fact the many animal facilities are located in basements, where LFN components may reach significant amplitudes. If fine biochemical pathways are under study, and LFN is present but not monitored, how reliable are the results?

Two Anecdotal Stories of False Controls

The Technical Drawing Division, at OGMA, seemed to be an excellent location from which to select a comparison population, also employed at OGMA, but not exposed to occupational LFN. A 34-year-old male, with just this occupational profile, exhibited abnormal brain potentials, consistent with values obtained for VAD patients (Castelo Branco et al., 1999b). Without his knowledge, his residential area, means of transportation and leisure activities, were investigated for possible sources of LFN noise. None were identified. Upon inquiry, his family and friends described him as reserved and quiet, but with sudden episodes of verbal aggressiveness, normally triggered by acoustic events. He was intolerant of any type of sound, including music and, like many others diagnosed with VAD, would complain of "hearing too much". A later audiogram disclosed losses in the lower frequencies, as with other VAD patients. All other VAD-related diagnostic tests came back positive: brain MRI revealed hyperintense foci in T2 of the deep white matter, and echocardiography revealed mitral valve and pericardial thickening. But where was he being exposed to noise? During the neurological examination, which revealed the existence of the palmo-mental archaic reflex, the man finally explained: his parents owned and operated a water mill, and lived in a house directly above. The permanent low hum of the operating water mill was a constant in his home, where he lived until the age of 26. Unfortunately, the mill has since been closed down, and acoustic evaluations of the mill in operation are no longer feasible.

Another interesting case is that of a 50-year-old executive director, who has worked in a Lisbon bank for the past 30 years. Apart from the usual air-heating and -cooling office devices, and urban traffic, the LFN exposure of this individual was not thought to be significant. However, echocardiography disclosed thickened pericardium and cardiac valves. The P 0.1 (CO_2) index value was below 30%. No symptoms were reported. Where was he being exposed to LFN? He lived in Montijo, a town across the River Tagus, and his daily car commute in heavy rush hour traffic takes 3 hours, approximately 100 Km. His cars have been equipped with diesel engines. In 1990, he restored his house in Galiza, Spain, just north of the northern Portuguese border and, since then, drives up there every weekend, approximately 400 Km each way. On a weekly basis, this man covers more 1500 Km in his diesel-engine cars. [Figure 5] compares the frequency distribution of a gasoline automobile with that of the Airbus-340 cockpit. The data strongly suggest that the source of this man's LFN exposure is the large amount of hours spent driving. Acoustical studies in his specific car models are still underway.

Misdiagnosis of Vibroacoustic Disease Stress-related syndrome

One of the most common commentaries about the signs and symptoms included in the Mild and Moderate Stages of VAD is their similarity to many generalized stress-related syndromes [Table 1]. Although a cursory view might suggest this, a more in-depth approach demonstrates that this is not the case. VAD is specifically characterized by an abnormal proliferation of extra cellular matrices in the absence of an inflammatory process. Lowered cortisol levels and elevated peaks of circulating norepinephrine were observed in LFN-exposed workers (Sobrinho et al., 1989), as well as, changes of auditory evoked responses (Castelo Branco, 1988) and of endogenous potentials that were correlated with CNS lesions - hyperintense foci in T2 of the subcortical and periventricular white matter, basal ganglia and brain stem (Pimenta et al., 1999). To the authors' knowledge, this is not consistent with stressrelated syndromes reported in the medical literature.

LFN exposure is more analogous to extreme stress situations, where similar brain lesions and cognitive impairment have been observed (Martinho Pimenta et al., 1992). Also, disseminated intravascular coagulation is frequently the only abnormal autopsy finding in young paratroopers, deceased during military training exercises - an extreme stress situation - giving credence to the popular expression, "it was a blood-curdling experience" (Castelo Branco, 1992). In LFN-exposed workers, an increased rate of platelet aggregation has been identified, simultaneously with other LFN-induced pathology (Castelo Branco et al., 2003e). Hence, regarding VAD as some generalized stress syndrome is not a tenable position, given its inconsistencies with what is known to date about generalized stress syndromes.

Malingering

Another common occurrence among VAD patients is the incredulity of physicians when confronted with complaints

involving almost all organs and systems. OGMA medical records show that some physicians scribbled "malingerer" on the side. In a candid exposure of his medical condition, Mr. Jonathan Arnot, age 40, a ship machinist from Scotland and diagnosed with VAD, wrote how the suspicion of

malingerer greatly affected his life:

"I had often been suspected of malingering (…) The social implications of being considered a malingerer, even on behalf of family members employed within the health industry, were quite demoralizing. (…) Without a diagnosis I was left in a no-man's-land where none of the medical specialists could suggest treatment. I felt I was left to see whether my symptoms developed further into an accepted illness, or if they would just resolve themselves with the passage of time. (…) I felt that doctors prejudged my case and assumed that I was either looking for a sick note to have time off work, or that I was trying to build a case to sue someone. Neither of which was anywhere near the truth, I simply could not afford to fall ill (…) Loss of self-esteem, and loss of standing in the eyes of my children and friends must also be taken into account. Social exclusion due to the lack of spending cash, and the emotional effect of the constant suggestion that I was just malingering are merely a few of the actual costs of falling ill with an occupational illness that is not yet proscribed in the UK." (Arnot, 2003).

Mr. Arnot exhibited very thickened cardiac structures (particularly the pericardium), a P 0.1 (CO_2) index of 38%, and increased latencies of P3 endogenous potentials, all consistent with the VAD clinical picture.

In general, physicians are not sufficiently knowledgeable to question the patient as to his/her occupation. Even if the patient works in the home, the residential location is rarely questioned in terms of acoustic environment. In fact, the insistence that acoustic phenomena only affect humans via the auditory system is helping to jeopardize the health of many young men and women. What neurologist sends a patient diagnosed with epilepsy to receive an echocardiogram? Skepticism as to the existence of a whole-body pathological entity caused by acoustic phenomena has been immense (von Gierke and Mohler, 2002). And yet, for decades, scientists have been gathering evidence supporting just that notion (Alves-Pereira, 1999). Sometimes, scientists say they first encountered VAD within the military in the 1970s (Brenner, 2003). Additionally, some VAD cases have been misdiagnosed as Chronic Fatigue Syndrome.

Dose-responses

Dose-responses for LFN exposure have not yet been established. Waiting for dose-response values to accept the existence of a disease does not seem to be an ethical, nor logical, course of action. In truth, obtaining dose-response values for LFN-exposed humans, considering its aforementioned ubiquitous nature, is a daunting task. Dosimeters specifically designed to evaluate LFN have not yet been developed and, as previously mentioned, legislated noise assessment procedures do not contemplate LFN as a hazard. Therefore, LFN dose-response values for humans are, most probably, some years (and Euros) away. However, in LFNexposed animal models, insight into doseresponses has already been obtained (Castelo Branco et al., 2003c). In Wistar rats exposed to continuous LFN for 48 hours, and then kept in silence for up to 7 days, tracheal epithelia of exposed and controls only became indistinguishable after 7 days of post-exposure silence (Castelo Branco et al., 2003c, 2003f). Wistar rats that were gestated and born in LFN, and subsequently kept silence for one year, still exhibited visible and dramatic damage of respiratory epithelia after the year in silence (Castelo Branco et al., 2003c, 2003g). The implications of these studies are far-reaching and speak for themselves, especially if one considers that many female workers carry their pregnancies to term while working in LFN-rich environments.

As a final note on dose-responses, it must be recognized that different organic tissues possess different acoustic properties, i.e., the acoustic impedance of lung tissue is different than that of the liver, and the resonant frequency for the brain is different than that for the bladder. Thus, doseresponses must be established on the basis of the frequency of the acoustic event. An individual working in a LFN environment where there is a predominance of infrasound (is not equivalent to stating that 70% will develop Stage III disabilities. The foremost concern is to prevent the development of disabilities that incapacitate individuals for further professional activity. Studies have indicated that, without prevention, approximately 5% of occupationally LFN-exposed individuals develop pathologies severe enough to require early disability retirement (Castelo Branco et al., 1999b).

At OGMA, from 1980 to 1989, 21 aircraft technicians received compulsory early disability retirement. In 1989, on the heels of the echocardiography results based on 1987 autopsy findings (see above), a screening and monitoring medical protocol was developed for all LFNexposed personnel. All incoming job candidates received echocardiograms as part of the routine physical examination. If pre-existing thickening of cardiac structures were identified, incoming job candidates would not be hired for jobs that implied working in LFN-rich environments. All LFN-exposed employees who already worked at OGMA began to receive annual echocardiograms, endogenous evoked potentials, and blood pressure was closely monitored. If and when LFN-exposed workers developed very thickened cardiac structures, and/or shifts in the P3 endogenous component to frontal positions, and/or difficult to control and unstable (labile) blood pressure, then they were removed from the LFN-rich work environment and placed at another, non-LFN-rich workstation. From 1989-1996 there were zero compulsory early disability retirements among LFN-exposed personnel (Castelo Branco et al., 1999b).

Recovery periods should also be an integral part of any prevention programme against LFNinduced pathology. For personnel that must remain more than the usual 8 hours within a LFN-rich environment, extended recovery periods, i.e., periods away from the LFN-rich environment, should be mandatory. Acoustic materials that impede the propagation of LFN are also in development by several teams worldwide, and might provide future answers to protect workers form this agent of disease. Lastly, it should be strongly emphasized that the development of LFN-induced pathology is caused by a cumulative effect of LFN exposure, and whether the source is occupational, or not, is irrelevant to the biological organism. Moreover, the evolution of VAD will be directly linked with the overall exposure received from all LFN-rich environments to which the individual is exposed, occupational and/or environmental and/or leisurely.

Current Working Hypotheses

Studies that describe acoustic environments merely in terms of an overall dB-level cannot be scientifically compared to those that provide frequency distributions analysis.

[Figure 4] and [Figure 5] compare the frequency distribution obtained in the cockpit of the Airbus-340 at cruise flight, with that obtained within a subway and a common passenger vehicle, respectively. See [Table 3] for overall average values. For the subway, the dBA-level was 70.9 and for the car it was 71.2. These acoustical environments are considered comparable by the scientific community at large. In fact, they are not. dBLin levels were 93.6 for the subway and 100.3 for the car. The difference between dBA and dBLin levels, and the lack of usefulness of dBA measurements within the context of LFN-induced pathology, has been extensively discussed elsewhere (Alves-Pereira et al., 2003a; 2003c; Alves-Pereira, 1999). The dBA value measures the overall average amplitude of the acoustical energy that is being captured (i.e. heard) by the human auditory system, and its usefulness is directly (and exclusively) related to the avoidance of hearing impairment. The dBLin value measures the overall average amplitude of the acoustical energy present in the environment, i.e., it measures the amplitude of what is actually present, and not just what can be heard. Looking at the distributions of both environments [Figure 4][Figure 5], it is clear that within the 1.6-500 Hz range, the car has higher levels at all bands than the cockpit. This is not the case with the subway. Hence, two situations arise: a) it is not scientifically sound to compare the results of noise-related studies that describe their acoustical environments merely in terms of a dBlevel measurement (i.e., without a frequency spectrum analysis), and b) the results of noiserelated studies that do not report the frequency distribution of their acoustical environments cannot be compared to those that do.

Individual susceptibility is a confounding factor

Individual susceptibility was identified early on as a important factor influencing symptom severity, and clinical evolution (Castelo Branco, 1989). Several parameters were evaluated, such as blood and tissue compatibility markers, in order to search for a LFN susceptibility indicator. To date, none have been formally identified (Castelo Branco and Rodriguez Lopez, 1999). Animal models gestated and born in LFNrich environments still exhibit severe respiratory tract damage, even after one year of post-birth continuous silence (Castelo Branco et al., 2003g).

Moreover, they also exhibit behavioral differences when compared with those LFNexposed animal models that were not gestated in LFN-rich environments. Hence, it is suspected that the situation of the individual's mother during pregnancy is one factor (of perhaps several) that may substantially contribute to an increased individual susceptibility to LFN. In ongoing research projects, the VADquestionnaire now includes questions pertaining to this matter. If occupational LFN exposure is the focus, then non-occupational LFN exposure can also introduce a confounding factor. As is shown in [Figure 1],[Figure 2],[Figure 3],[Figure 4],[Figure 5], LFN is ubiquitous. Hence, VAD-related questionnaires must explore all habitual and non-habitual locations where individuals may be exposed to LFN, including in utero.

LFN environments with acoustical energy predominantly within the infrasonic range (et al., 2001). In a subsequent acoustical analysis of both cockpit and cabin, the cockpit revealed statistically significant higher levels of infrasound than in the cabin (Alves-Pereira et al., 2001). Infrasound in the cockpit varied with altitude, airspeed and aircraft model, which indicates that much of the infrasonic energy present in the cockpit is due to the impact of the airflow on the leading edge of the aircraft (Alves-Pereira et al., 2001).

The onset of auto-immune diseases is accelerated by LFN exposure.

As discussed above, in the Associated Pathology of VAD, auto-immune diseases, particularly lupus, are very common among LFN individuals (Torres et al., 2001; Araujo et al., 2001; Matsumoto et al.,1992, 1989; Jones et al., 1976; Soutar et al., 1974; Lippmann et al., 1973). One of the reasons may be the presence of nonapoptotic cellular death, with no inflammatory process, seen in the pericardial fragments of VAD patients (Castelo Branco et al., 1999a, 2001, 2003a,b).

The respiratory system is a target for LFN.

Four VAD patients had atypical cases of pleural effusion that persisted in spite of therapy. Three of these cases were of unknown origin, although the fourth may have been caused by diphenylhydantoin (Castelo Branco, 1999a). The follow-up recovery periods were very prolonged, even in the case where diphenylhydantoin was suspended. Treatment took several months, and recovery was not only slow and irregular, but no conclusion was ever reached about the aetiology or choice of treatment. In the 1987 autopsy, focal lung fibrosis was identified, however no importance was attributed to this finding since chemicals, fumes and dusts were assumed to be present in this man's occupational environment (Castelo Branco, 1999a). In 1992, still concerned about the enigmatic cases of pleural effusion, animal models were used to study the respiratory tract response to LFN exposure. In LFN-exposed rodents, the amount of tracheal cilia was visibly reduced, and subsequent formal morphometric studies confirmed this feature (Oliveira et al., 2002). Tracheal subepithelial fibrosis was also identified (Castelo Branco et al., 2003c). Structural changes of the lung parenchyma included irregular distribution of thickened alveolar walls, dilated alveoli, and irregularly distributed fibrous foci (Castelo Branco et al., 2003c). Pleural cells lost their phagocytic ability, and the pleural parietal leaflet had a marked reduction in the amount of microvilli per mesothelial cell (Oliveira et al.,1999). Subsequently, respiratory function tests and high resolution CT scan of the lung were administered to LFN-exposed workers, with and without respiratory symptoms. Focal lung fibrosis and air-trapping were identified in these workers, independent of the existence of respiratory complaints (Reis Ferreira et al., 1999). Other authors have described the immediate subjective effects of large amplitude LFN tones on the respiratory system that included coughing, gagging sensation, and awareness of chest wall pressure (Mohr et al., 1966; Cole et al., 1966). An in-depth review of noise and the respiratory system has been reported elsewhere (AlvesPereira et al., 2003c).

LFN-exposure specifically causes squamous cell carcinomas of the respiratory tract.

To date, 100% of the respiratory tumours in VAD patients have been squamous-cell carcinomas: 10 in the upper right lobe of the lung (7 smokers) and 2 in the glottis (1 non-smoker) (Castelo Branco, 2001). This hypothesis has been further corroborated by the observation of metaplasia and displasia in the respiratory epithelium of LFN-exposed Wistar rats (Castelo Branco et al., 2003c; 2003g). In the general population, squamous cell carcinomas of the lung account for 40% of all lung tumours (Skuladottir, 2001). However, cancer-related epidemiological studies do not usually describe the breakdown of tumour-type, which is very unfortunate. Global cancer statistics, without a breakdown of tumour-type, do not contain the essential, and crucial, information required for any in-depth statistical study, and the results can be misleading. Among VAD patients, the incidence of lung cancer, in general, is about the same as that of the Portuguese population, but in VAD patients, all tumours are located in the upper right lobe, and all are squamous-cell carcinomas (Castelo Branco, 2001). This is not equivalent to saying that all squamous-cell carcinomas all triggered by LFN-exposure, because certainly other agents might also induce the appearance of this type of respiratory tract tumour. What the date does demonstrate is that LFN-induced respiratory tract tumours are all of a single type: squamous cell-carcinomas.

Actin and tubulin based structures are particular targets for LFN.

Microvilli are composed of actin filaments, as are the streocilia in cochlear auditory hair cells. In LFN-exposed animals, both cochlear stereocilia and respiratory tract brush cell microvilli become fused structures (Castelo Branco et al., 2003c, Alves-Pereira et al., 2003b). A first approach might suggest that the commonality of these structures may be their finger-like, somewhat cylindrical shapes. However, cilia, found in the respiratory tract and in the pericardium, exhibit an entirely different behavior in the presence of LFN. Cilia in the pericardial fragments of VAD patients simply cease to exist (Castelo Branco et al., 2003a,b; 2001; 1999a). In the respiratory tract of LFNexposed animals, cilia appear sheared, as if clipped by scissors, and some images even captured these apparently sheared cilia lying upon the epithelial surface (Castelo Branco et al., 2003c). Shaggy cilia and completely bald ciliated cells were also observed in LFN-exposed rodents. In two VAD patients (one non-smoker), scattered areas of damaged tracheal cilia were identified, and multiple ciliary axonemes were seen surrounded by the same membrane (Reis Ferreira et al., 2003c).

Elevated annoyance levels to noise are a sign of previous, excessive LFN exposure.

Cochlear stereocilia are actin-based structures that, in Wistar rats, fuse as a response to LFN exposure (Castelo Branco et al., 2003c). Rats are particularly sensitive to the sound of a "blown kiss" and react by jerking their heads and becoming tense. After LFN-exposure, the "blown kiss" causes them to rise on their hind legs, often falling backward, with tremors. Fused cochlear stereocilia, if it also occurs in humans, may explain the unusual auditory complaints of VAD patients, such as, "I hear too much; I can't stand any type of noise, not even music" (Castelo Branco,1999b). If fused among themselves and to the tectorial membrane, cilia cannot freely vibrate as is intended when the sound pressure wave is transduced within the cochlea (Alves-Pereira et al., 2003c). In fact, by becoming a rigid structure, any attempt at vibrating them might, understandably, produce discomfort. How closely related this phenomenon is to the concept of "annoyance" is still unclear. However, a relationship is clearly suggested,

especially since annoyance has already been specifically associated with the presence of LFN (Persson-Waye and Rylander, 2001).

The whole-body response to excessive LFN exposure can be explained by principles of biotensegrity

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At a cellular level, the pericardial mesothelialcell (MC) layer exhibits a peculiar morphological behaviour. The MC layer consists of a one-cell-deep surface, and is in direct contact with the pericardial sac. Hence, it is critical to the sliding effect necessary to an intact cardiac cycle. MC interconnect laterally with each other via cytoskeletal intermediate filaments and desmosomes. In pericardial fragments obtained from VAD patients, MC are seen in a process of extrusion from the surface layer into the pericardial sac (Castelo Branco et al., 2003a,b). Desmosomes are no longer evenly distributed along the lateral edges of MC, and instead are concentrated, in groups of more than two, in the upper portions of the MC lateral borders. The lower portions seem to be forming gaps, with great plasticity, in which microvilli are identifiable (Castelo Branco et al., 2003a). Biotensegrity systems can absorb external forces, and redistribute them throughout a network of tension and compression elements, but with no torque or bending moments (Wang et al., 1997). Consider the MC layer as a structural surface composed of individual viscoelastic elements (the MC interconnected by cytoskeletal intermediate filaments and desmosomes) and that has to cope with abnormally large mechanical forces. Extrusion of MC into the pericardial sac strongly suggests that the MC layer is attempting to maintain the structural integrity, despite the abnormal biomechanical conditions.

Final Commentary

The agent of disease has already been identified - Low Frequency Noise.

Specific LFN effects have already been well defined: abnormal growth of extra-cellular matrices, in the absence of an inflammatory process, seen in both cardiovascular and respiratory system structures, in both LFNexposed human and animal models.

The genotoxicity of LFN exposure has been demonstrated in both human and animal models.

Non-invasive diagnostic methods have already been defined: echocardiography to visualize thickened cardiac structures, P 0.1 (CO_2) index to measure the dramatically reduced respiratory drive, and evoked potentials that disclose important topographical changes and increased latencies in the P3 and N2 components, both indicative of cognitive impairment.

Large-scale epidemiological studies are still unpublished, in-depth studies of LFN-induced physiopathology are lacking, and case-control studies have not yet appeared in the medical literature. In fact, to the authors' knowledge, no other independent team has published results on echo-imaging studies on LFN-exposed individuals. Why? One of the main (scientifically-related) reasons is that LFN-induced is not "high-priority" topic in most scientific forums, hence grant approval rate for LFN-related studies is very low. Other, more political and financial reasons exist, however they are, of course, beyond the scope of this report.

The bottom line is: VAD is not acknowledged as a pathological entity, and individuals who exhibit VAD clinical pictures are malingerers (if workers) or neurotic (if females and/or housewives). At best, they are considered "overly sensitive" individuals. Moreover, since LFN exposure is not considered a health hazard by the authorities, it is rarely evaluated. Additionally, LFN-related studies are not "fashionable", and thus grant money for this field is practically non-existent. Given the data collected to date and the worldwide suffering of

millions of LFN-exposed citizens, this status quo situation is unethical, unsustainable, and downright obscene.

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