ScienceMED

ISSN 2039-4632

an International Journal of Medical Sciences

MEDIMOND

INTERNATIONAL PROCEEDINGS vol. 4, n. 1.2013

ScienceMED
an International Journal of Medical Sciences

ISSN 2039-4632

Director and editor-in-chief
Musiani Irio
Medimond s.r.l. - Via G. Verdi 15/1, I-40065 Pianoro (Bologna)
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This journal was printed in July 2013 by EDITOGRAFICA s.r.l.,
www.editografica.com.

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Miscellaneous

ScienceMED, vol. 4, 1.2013, 1-8, Bologna (Italy)

From Pulec's Cervical Tinnitus to Levine's Somatic Tinnitus

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Abstract

Somatic tinnitus is a sub-group of tinnitus suffers. It was described by Pulec et al.in 1978 as "cervical tinnitus" , considered as a consequence of degenerative changes in the cervical spine that could be, at least temporarly, reduced by injection of local anesthetic into tender areas of the neck. This clinical entity was forgotten until Levine et al. in 2007 introduced the Somatic Tinnitus Syndrome (STS)in which tinnitus is associated to a somatic disorder involving the head and neck. They presented the anatomical basis for the auditory-somatosensory interactions and showed how auditory neurons respond to somatosensory stimulation.

Muscle--skeletal system could be a chronic stress source. In this way muscle-skeletal disorders can pathologically integrate with auditory disturbances increasing tinnitus. In this way Stress Reaction Tinnitus (SRT) model could be implemented into Somatic Tinnitus Syndrome (STS) model and Tinnitus School can acts through fitted physiotherapy aimed to a patient-oriented treatment of selected tinnitus patients.

Somatic Tinnitus, generally, is a well treatable condition by means of manipulations, physiotherapy and physical exercises, or at least, removal of somatic component of patient's tinnitus significantly decreases tinnitus annoyance and improves quality of life.

Keywords: *tinnitus, somatic tinnitus, cervical, tinnitus school*

Introduction

Somatic tinnitus is a sub-group of tinnitus suffers. It was described by Pulec et al.in 1978 [1] as "cervical tinnitus" , considered as a consequence of degenerative changes in the cervical spine that could be, at least temporarly, reduced by injection of local anesthetic into tender areas of the neck. This clinical entity was forgotten

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until Levine et al. [2] in 2007 introduced the Somatic Tinnitus Syndrome (STS)in which tinnitus is associated to a somatic disorder involving the head and neck. They presented the anatomical basis for the auditory-somatosensory interactions and showed how auditory neurons respond to somatosensory stimulation.

More specifically, somatic tinnitus suffers frequently present modulation of their spontaneous tinnitus through appropriate stimulation of trigger points in cervical and shoulder muscles. Somatic Tinnitus occurs when the patient feels the effect of head and neck muscle contractions, changing the intensity or quality of tinnitus, for instance during clenching the teeth or head rotation. In these cases, tinnitus is modulated by stimulation of the somatosensory system as a result of muscle contractions. This is not surprising because the auditory system is part of the most complex sensory-motor system involved in the head position regulation, necessary to provide gravitation reference, prerequisite for a correct orientation of the human subject in the environment. The brainstem and cerebellum are the main sites of integration of multi-sensorial information from the inner ear [3], retina and proprioceptors regarding head position, body position, gravity, visual landmarks and movement of the jaw, the tongue, and the pharynx.

Stress is known to be a significant factor influencing the clinical course of tinnitus. Auditory system is in fact particularly sensitive to the effects of different stress factors (chemical, oxidative, emotional, …). Horner [4] described different stages of auditory pathways reaction to stress: alarm, resistance and exhaustion. Individual characteristics of stress reaction may explain different aspects of tinnitus in various patients with different responses to treatment, despite similar audiological and ethiological factors. A model based on individual reactions to stress factors (Stress Reaction Tinnitus - SRT -Model) could explain tinnitus as an alarm signal. In 2006 Alpini and Cesarani [5] described a therapeutic proposal based on SRT Model, through an integrated approach to management of patients suffering with chronic tinnitus. Educational aspect was emphatized and thus the approach was named Tinnitus School, that is a three-phases program (counselling, training, home training) mainly based on fitted physiotherapic protocol. [6]

Muscle--skeletal system could be a chronic stress source. In this way muscle-skeletal disorders can pathologically integrate with auditory disturbances increasing tinnitus. In this way Stress Reaction Tinnitus (SRT) model could be implemented into Somatic Tinnitus Syndrome (STS) model and Tinnitus School can acts through fitted physiotherapy aimed to a patient-oriented treatment of selected tinnitus patients.

Somatic Tinnitus, generally, is a well treatable condition by means of manipulations, physiotherapy and physical exercises, or at least, removal of somatic component of patient's tinnitus significantly decreases tinnitus annoyance and improves quality of life.

Diagnosis of Somatic Tinnitus

Diagnosis must combine investigation of auditory condition and somatic cervico-cephalic condition. Diagnosis is three-folded:

1) Identification of eventual auditory damage and main tinnitus characteristics

2) Forceful maneuvers of the neck and the mouth (so called somatic tests) to identify somatic component of tinnitus: the more prevalent the somatic component the higher the possibilities to cure tinnitus

3) Identification of emotional and cognitive aspects of tinnitus induced disturbances

2.1 Identification of eventual auditory damage and main tinnitus characteristics

Pure Tone Audiometry and Tympanometry are the basic steps to identify hearing loss. The loudness of tinnitus can be estimated by asking the individual to adjust an external sound so as to match the loudness of the tinnitus. One method is for the listener to first select a sound that is similar to their tinnitus. For example, if the tinnitus is tonal, the listener might adjust the frequency of a pure tone until it matches the pitch of their tinnitus. Then, the external tone is adjusted in level so as to match the loudness of the tinnitus. For the scope of somatic tinnitus assessment Feldman test [7] and Loudness Discomfort Level test [8]are enough to investigate auditory/somatic interaction under a therapeutic point of view.

2.2 Forceful maneuvers

Levine et al. [2] proposed to identify somatic components of tinnitus through a series of forceful manouvres or pressure of some parts of the head or the neck, during which patients has to note modification of tinnitus loudness or pitch:

a) CLENCH - OPEN JAW also AGAINST RESIST – PROTRUDE also AGAINST RESIST –RETRACT

b) Right and left JAW DEVIATION also AGAINST RESIST

c) Pressure against FOREHEAD, BACK, right and left TEMPLE

d) Flexion of the Head against forehead resist – Extension of the head against Vertex resist – Right and left head Turn against resist

e) Pressure on JAW – VERTEX – right and left Sterno-Cleido-Mastoideus (SCM) – Right and left SPLENIUS PRESSURE – right and left MASTOID PRESSURE

f) Right and left PINNA PRESSURE and PINNA PULL

g) Furthermore, examination protocol includes:

h) Neck Range of Movement

i) Palpation of right and left Trapezius, Temporalis, Massetter, Medial Pterygoid. For each muscles bulk tender and tension are subjectively quantified ranging from 0 to 5

We have simplified the examination protocol as follow:

1) Jendrassik maneuver

2) Clench teeth together – forced opening of the mouth and Protrude jaw with and without restorative pressure

3) With the head in the neutral position, contractions to resist pressure applied by the examiner to Forehead and Occiput

On the basis of the results of these main manouvres an accurate evaluation/palpation of the Temporo Mandibular Joint (TMJ) and stomatognatic muscles and/or cervical and dorsal spine according the examination criteria of Manual Medicine as described elsewhere [9] is therefore performed. Generally speaking, Manual Medicine examination is mainly aimed to identify trigger and tender point of the facial and cervico-dorsal muscles. Trigger points are described as hyperirritable spots in skeletal muscle that are associated with palpable nodules in taut bands of muscle fibres. Trigger point are small contraction knots and a common cause of pain. Compression of a trigger point may elicit local tenderness, referred pain, or local twitch response. It is common to

induce transient tinnitus when stimulating trigger points in trapezius muscle. A tender point hurts to the touch and causes some degree of pain in that area, while a trigger point may not necessarily be painful to the touch but causes a degree of pain (or tinnitus in this specific field of investigation) to be felt in another area. Furthermore, Manual Medicine looks for so called Painful Minor Intervertebral Disorders (PMID), in these cases, paying particular attention to the cervical and dorsal spine.

Particular attention is also paid to Temporo-Mandibular-Disorders (TMDs) very often underdiagnosed in Tinnitus patients. TMDs are a group of related disorders of the masticatory system (the masticatory musculature and the temporomandibular joint). The most frequent symptom is pain, usually localized in the muscles of mastication, the preauricular region, and the temporomandibular joint (TMJ). Patients often complain of jaw ache, earache, headache, and facial pain. In addition to pain, patients with these disorders frequently have limited or asymmetric jaw movement and joint sounds that are described as clicking or crepitus.

Jendrassik manouvre is useful to identify aspecific activation of tinnitus while Manual Medicine examination procedure provides the basis of the manipulative treatment. When TMD are prevalent manipulative and physical treatments have to be combined with adequate stomatognatic therapy.

2.3 Identification of emotional and cognitive aspects of tinnitus induced disturbances

Tinnitus Reaction Questionnaire (TRQ) [10] is useful to identify the tinnitus stress induced phase of a specific patient. TRQ is a self-reported scale designed to assess perceived distress associated with tinnitus. To determine individual Tinnitus specific reaction beside TRQ, Tinnitus Cognitive Questionnaire (TCQ) [11] was adopted. Regarding general stressor identification, we adopted the CAPPE questionnaire [12] that investigates the presence of different kind of stressors: Chemical (prolonged expositions to solvents, assumptions of ototoxic drugs), Acoustic (noise exposure, acoustic neuroma, otosclerosis, hearing loss), Pathologies (diabetes, thyroiditis, autoimmune diseases), Physical (professional stress, worsening of tinnitus during physical exercises), and Emotional (sleep disorders, job change, depression). The general perceived stress is quantified through Perceived Stress Questionnaire (PSQ) [13]. It is designed to represent the subjective perspective of the individual. ("You feel...").

2.4 Selection of the treatable patients

The inclusion criteria are:

1) Acute or Chronic Tinnitus with TRQ less than 80
2) CAPPE 's item "increasing with physical exercise" positive answer
3) PSQ score at least 15 as total score OR 4-5 score in "tension" sub-scale
4) Patient's tinnitus modulated by somatic manoeuvres as described above
5) No tinnitus modulation by Jendrassik manoeuvres. In our experience modulation by clenching, neck forceful flexion,… AND Jendrassik modulation means a no-specific facilitation of tinnitus perception to be distinguished from specific, treatable, somatic involvement
6) Trigger or tender point in the muscles, specifically activated during forceful somatic manoeuvres, e.g. masseter or anterior temporal regarding clenching, sterno-

cleido-mastoideus regarding neck flexion or rotation, and so on Feldman masking curve, LDL level, TRQ, PSQ and TCQ represent the outcome measures

Treatment of Somatic Tinnitus

Treatment is mainly based on so called Tinnitus School as described elsewhere [14,15]: Tinnitus School is a five step program as follow

1. amelioration of lifestyle through adequate counselling based on case history and CAPPE questionnaire

2. removing cervico-cephalic sensory-motor disturbances, by means of Manual Medicine techniques [9] including also High Velocity Low Amplitude vertebral manipulations, directly performed by the physician.

3. leading the patient to an awareness of own body and learning breath and neck tension control, through physical exercises performed with a physiotherapist in a gymnasium. Tinnitus School physiotherapy program is constituted by ten sessions subdivided into three sessions per week along two weeks followed by two sessions per week along two other weeks. The first step is to prepare the patient to cooperate in a complex program involving movement, thinking and learning. Muscle-skeletal impairments [16] are often provoked or associated to tension and anxiety, that is why head and neck disorders have to be treated before training. Furthermore, it is more necessary to begin treatment with simple relaxation exercises to manage patient's tension management. Physical Exercises are pointed to postural control because, in chronic somatic Tinnitus as well in WAST, the abnormal alignment of body parts with respect to each other and to the base of support, may be due to both musculoskeletal cervico-cephalic impairments and changes in patient's internal perception of the own sensations induced by pathological attention to tinnitus. Simple exercises have to be planned and they are generally pointed to mobilization of the pelvis, of the cervical rachis and the thoraco-lumbar spine. In some cases massages can be useful either to relax the patient or to mobilize joints, including Slow Velocity High Amplitude vertebral manipulations performed by the physiotherapist. Tinnitus School Protocols are shown in tab. I

4. shifting patient attention away from tinnitus, through home physical exercises [17,18,19,20]

5. Bibliotherapy. Self-help books exist for a wide variety of psychological problems. Studies of their value indicate that they can help individuals to make substantial improvements [21], on average about as much as psychotherapy. We propose to our patients the Italian version (Springer, Milan, 2012) of "Tinnitus: A Self-Management Guide for the Ringing in Your Ears". This self-help book by Henry & Wilson [22] is based on cognitive–behavioural principles, including educational information on tinnitus, cognitive reappraisal and restructuring, relaxation and stress management techniques, attention control techniques, use of self-instruction, making lifestyle changes, and maintaining gains.

Tab. I Tinnitus School Gymnasium Training Protocol

Supine (all the exercise are performed having patients' head comfortably lying on a pillow)

- Relaxation exercises with control of breathing improving consciousness of abdominal or thorax breathing: deep inhaling followed, after few seconds, by a forced exhaling pronouncing the word "one". This exercises is repeated 8-10 times

- Patients move the head, first slowly and then faster, in all directions focusing a target straight on the ceiling
- Patients take the right knee against the chest, then extend the leg and take the left knee against the chest. A gentle traction the flexed leg is performed by patient himself when the knee is taken against the chest
- Patients take both knees to the chest, contemporarily, helping, gently, with the hands
- Patients lift pelvis taking contemporary the arms extended over the head. Then patients re-takes arms along the body lowering the pelvis
- Patients grasp a stick. Then they extend the arms over the head and then return in primary position
- In the quadrupedal position, patients inhale and arch the back taking the head between the arms. Then they exhale retro-flexing the head and rotating the pelvis in hyperlordosis
- In quadrupedal position, patients extend contemporary the right arm and the left leg. Then repeat with the left arm and the right leg
- In prone position, patients lift their left arm and the right leg maintaining the forehead over the bed. Then they repeat with the right arm and the left leg

Sitting

- Patients move the head first slowly and then faster in all directions focusing on a target straight in front
- Patients look for three targets sited, respectively, in front, at their left and at their right. Then patients focus on the front target, then they move the head focusing the right-sited target. At last they rotate leftward the head maintaining the focus on the right-sited target
- Patients focus on the frontal target. Then they move the head leftward and focus the left-sited target. At last they rotate rightward the head maintaining the focus on the left-sited target
- Patients turn the head rightward and focus on a target on the lateral wall. Then they take the head straight maintaining focusing, through eyes counter-rotation, and count until 10
- Patients turn the head leftward and focus on a target on the lateral wall. Then they take the head straight maintaining focus on the target, through eyes counter-rotation, and count until 10
- Patients extend the right arm and lift their thumb. Thus patients move slowly the arm to-and-from before along an horizontal direction and then along a vertical direction. Patients pursuit the thumb with eyes only, first slowly and then increasing progressively the velocity of thumb displacement
- As above but moving contemporary also the head trying to maintain the eyes still
- Patients grasp a stick with both hands and take the stick behind the shoulder positioning the stick at level of cervico-dorsal junction. In this position they rotate to-and-fro the trunk maintaining the head still also focusing on a target straight in front. Rotation of the trunk have to be harmonic with quiet breathing
- Patients put the stick forward on the sternum at the level of the sterno-clavear joint. Then they perform rhythmic backward displacements of shoulders
- In this position they rotate to-and-fro the trunk maintaining the head still also through fixation of a target straight in front. Rotation of the trunk have to be harmonic with quiet breathing
- Paying attention to quiet breathing patients inspire. Then, exhaling, they bend forward taking the head on the right knee. They wait 10 seconds. Then, inhaling they return in sitting position.
- Paying attention to quiet breathing patients inspire. Then, exhaling they bend forward taking the head on the left knee. They wait 10 seconds. Then, inhaling they return in sitting position.
- Patients Inhale. Exhaling they bend forward to keep an object on the floor. Then they inhale and take it up over the head and then they fixate it for 10 seconds. Patients inhale. Exhaling they bend forward and take the object on the floor

Standing

- Patients focus themselves on a mirror and align correctly their posture. Thus they maintain quiet

equilibrium for 1 minute, paying attention to breathing; before they maintain eyes open and successively they close the eyes imagining the correct position in their mind. They remain in this position for at least 1 minute paying attention to breathing. Then they oscillate to-and-fro according to the breath rhythm, hearing the air that enter and then exits from the lungs

- Patients in quiet upright position fixate a target on a mirror. In this case they have two planes of fixation: the target and their image. Thus they have to be able to extract the correct fixation information from visual inputs. Then they oscillate to-and-fro according to the breath rhythm hearing the air that enter and then exits from the lungs
- Patients keep a little object and lift it over the head fixating it. Then they deeply inspire. Expiring, they bend forward taking the object on the floor. They wait 10 seconds and then, inspiring, they lift again the object over the head
- Patients take a little object over their head. Fixating the object they move it in small circles according to breath rhythm hearing the air that enter and then exits from the lungs

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ScienceMED, vol. 4, 1.2013, 9-15, Bologna (Italy)

Chronic Cerebrospinal Venous Insufficiency (CCSVI) IN Meniere Disease. Case or Cause?

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Abstract

CCSVI is the acronym for Chronic Cerebrospinal Venous Insufficiency, initially described by P.Zamboni, as being strongly associated with multiple sclerosis (MS). It is a syndrome characterized by stenosis of the internal jugular veins (IJVs) and/or azygous vein (AZ) with opening of collaterals and insufficient drainage.

Bavera PM carried out 823 Duplex exams on a control group of 60 patients without MS. As expected CCSVI was found only in few subjects of the control group, three, two females and one male, but all affected with Sudden Sensorineural Hearing Loss (SSHL).

Successively, we reported a case of bilateral SSHL with vertigo, showing evidence of the CCSVI pattern at Duplex examination (not associated with MS). To the best of the authors' knowledge, this kind of association has never been reported.

We studied 52 patients affected with cochleo-vestibular disturbances subdivided into two groups of out-patients:Definite unilateral Meniere (Men): 12 subjects (8 males and 4.females, mean age 41,6.yy) according to international AOO-HNS 1995 diagnostic criteria - No-Meniere (No-Men): 14 subjects (6.males and 8 females, mean age 44,7.yy) affected with unilateral cocleo-vestibular impairment

A third group of subjects have been considered, as a "normal" group, 13 patients (8 females and 5 males, mean age 45,5 yy) affected with Benign Paroxismal Positioning Vertigo (BPPV) with cochlear involvement

Asymmetrical artherious flow in VA or CA was revealed in 2 Men 9 no-Men and 1 BPPV, respectively 12,5 - 60,7 - and 8,6 %. Differences between Men and No-Men and between each of this group with respect to BPPV were highly significant ($p<0.001$). Asymmetrical venous flow in IJV or VV was detected in 9 patients in MEN group and in 4 in no-MEN and 2 BPPV, respectively 79 - 28,5 and 13 %. Differences between Men and No-Men and between each of this group with respect to BBV were highly significant ($p<0.001$)

Key words: *CCSVI, Meniere Disease, Vertigo , Hearing loss*

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Introduction

As a matter of fact the venous outflow of the neck has aroused interest, and importance, mostly in these last three years after the so-called Zamboni method aimed to detect and study " Chronic Cerebrospinal Venous Insufficiency" (CCSVI) [1]. This type of exam and problem, based on detection of abnormal venous outflow from the head and neck, is principally linked with multiple sclerosis disease. It is characterised by multiple stenoses of the extracranial venous draining pathways, i.e. the internal jugular veins and the Azygous veins, which lead to collateral formation, alteration of the blood-brain barrier. It could be diagnosed by means of MRI digital Venography and, especially, Duplex examination of cerebral and cervical vein system. [2,3]

Abnormalities of cerebro-spinal venous flow have been described also in no-MS patients. For example Koerte et al. [4] performed a 2D time-of-flight MR-venography of the upper neck region to visualize the venous vasculature in patients with migraine. They showed a higher prevalence of dense secondary extracranial venous networks and a significantly larger percentage of venous outflow through secondary channels, through epidural, vertebral, and deep cervical veins.

Bavera PM [5] carried out 823 Duplex exams on a control group of 60 patients without MS. As expected CCSVI was found only in few subjects of the control group, three, two females and one male, but all affected with Sudden Sensorineural Hearing Loss (SSHL).

Successively, we reported [6] a case of bilateral SSHL with vertigo, showing evidence of the CCSVI pattern at Duplex examination (not associated with MS). On the basis of these experiences we decide to investigate Cerebrospinal Venous system in Otoneurological patients even if not associated with Multiple Sclerosis.

In order to clarify the role of venous drainage in Meniere Disease we compared cervico-cephalic emodynamic (arterial and venous flows) in three groups of patients affected with vertigo, Meniere Disease (MD), no-Meniere and Benign Paroxismal Positioning Vertigo (BPPV).

Material and Methods

We studied 52 patients affected with cochleo-vestibular disturbances subdivided into two groups of out-patients:

- Definite unilateral Meniere (Men): 12 subjects (8 males and 4.females, mean age 41,6.yy) according to international AOO-HNS 1995 diagnostic criteria [7]
- No-Meniere (No-Men): 14 subjects (6 males and 8 females, mean age 44,7.yy) affected with unilateral cocleo-vestibular impairment

A third group of subjects have been considered, as a "normal" group, 13 patients (8 females and 5 males, mean age 45,5 yy) affected with Benign Paroxismal Positioning Vertigo (BPPV) with cochlear involvement

All of them underwent to a complete audio-vestibular investigation by the same audiologist (MV)) according to international acceptd protocol [8] . Diagnosis was posed by the same otoneurologist (A.DC).

ECD was performed by the same specialist (BPM) and two test were performed:

1) Arteries test. Flow of vertebral artery (VA) of both sides have been investigated both

in static and dynamic positions in order to evaluate the variations of arterial flow due to head and neck movements. The flow, static and dynamic, of the cochlear artery (CA) of both sides have been investigated, too, according to the method described by Belcaro and Nicoalides [9] with the patient is completely lying flat on his back in the most comfortable way, with a low pillow, searching absolute neck relaxation to avoid possible muscular contraction. The Duplex access to "find" the cochlear arterial system may differ from one patient to another and should be carried out from a posterior and anterior projection of the ear and "working" a lot on the machine's capacities. It isn't only a matter of what is seen but also of what is heard and transformed into a spectral flow analysis The blood flow exam is mostly based on the CW scale more than on the imaging itself because of the small vessel dimensions.

ECD was considered abnormal when the vertebral and/or the cochelar artery presented a reduced flow in static and/or dynamic conditions at the same side of the affected ear at least of 50% with respect of the controlateral side

2) Veins test, according to the protocol described by Zamboni et al. [1]. The CCSVI protocol exam at 00° and 90° was carried out on informed and willing patients according to CCSVI diagnosis procedure.

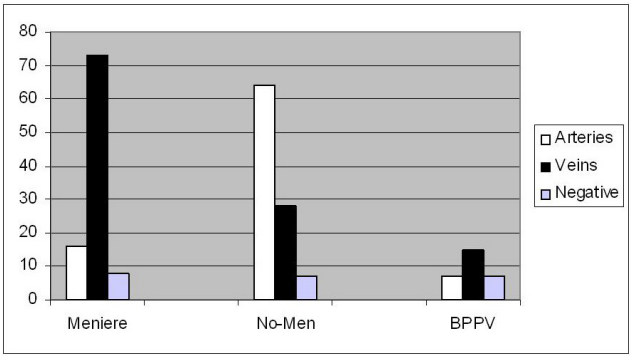
ECD was considered abnormal when at least two out five of Venous Haemodynamic Insufficiency Severity Score (VHISS) criteria were satisfied.

Results were discussed with an independent well-trained otoneurologist (HA). MEN vs no-MEN vs BPPV findings were compared by means of Student t-test and considered as significant at 0.005 p level.

Results

Asymmetrical artherious flow in VA or CA was revealed in 2 Men 9 no-Men and 1 BPPV, respectively 12,5 - 60,7 - and 8,6 %. Differences between Men and No-Men and between each of this group with respect to BPPV were highly significant ($p<0.001$).

Asymmetrical venous flow in IJV or VV was detected in 9 patients in MEN group and in 4 in no-MEN and 2 BPPV, respectively 79 - 28,5 and 13 %. Differences between Men and No-Men and between each of this group with respect to BBV were highly significant ($p<0.001$)



Tab.1: Figure shows the distribution of ECD abnormal tests in the three groups of patients. Artherious abnormalities are significant more represented in no-Men, venous abnormalities in Men, normal results in BPPV

Conclusions

Meniere's disease is a chronic illness that affects a substantial number of patients every year worldwide. The disease is characterised by intermittent episodes of vertigo lasting from minutes to hours, with fluctuating sensorineural hearing loss, tinnitus, and aural pressure. The primary histopathological correlate is endolymphatic hydrops. Paparella [10] used the notion of "lake-river-pond" to explain the occurrence of malabsorption of endolymph leading to hydrops. This notion describes the endolymphatic sac as a pond, with the vestibular aqueduct (the river) connecting it to the endolymphatic fluid space that is like a lake. When there is an obstruction near the endolymphatic sac or duct, a backlog of endolymphatic fluid is created, leading to hydrops.

The vertebral artery is a major artery in the neck, It branches from the subclavian artery, where it arises from the postero-superior portion of the subclavian artery. It ascends thought the foramina of the transverse processes of the sixth cervical vertebrae. Then, it winds behind the superior articular process of the atlas. It enters the cranium through the foramen magnum where it unites with the opposite vertebral artery to form the basilar artery (at the lower border of the pons). At the junction between the medulla oblongata and the pons two vertebral arteries joint into the basilar artery, forming the so-called the vertebrobasilar system, which supplies blood to the posterior part of circle of Willis and anastomoses with blood supplied to the anterior part of the circle of Willis from the internal carotid arteries.

The basilary artery ascends in the central gutter (sulcus basilaris) inferior to the pons and divides into the posterior cerebral arteries and the superior cerebellar artery. From the basilar artery arises the anterior inferior cerebellar artery (supplying the superior and inferior aspects of the cerebellum), as well as smaller branches for the supply of the pons (the pontine branches). In under 15% of people the basilar artery gives rise to the labyrinthine artery while, generally, the labyrinthine artery (then subdivide into cochlear and vestibular arteries), is a long slender branch of the anterior inferior cerebellar artery (more or less 85% cases) or basilar artery (<15% cases), arises from near the middle of the artery; it accompanies the vestibulocochlear nerve through the internal acoustic meatus, and is distributed to the internal ear.[11]

The veins of the vestibule and semicircular canals accompany the arteries, and, receiving those of the cochlea at the base of the modiolus, unite to form the internal auditory veins (or veins of labyrinth) which end in the posterior part of the superior petrosal sinus or in the transverse sinus. [12] The common modiolar vein enters the bony channel immediately adjacent to the aqueduct to become the vein of the cochlear aqueduct which in turn drains via the inferior petrous sinus into the Internal Jugular Veins (IJVs). Injury or occlusion of this vessel would be particularly significant since it is widely believed to provide virtually the entire venous drainage of the cochlea. [13] The cochlear aqueduct and the internal auditory canal communicate with the subarachnoidal space; in the guinea pig model, an occlusion of the veins of the cochlear aqueduct results in an increase of perilympatic endolymphatic pressure, a decrease of cochlear blood flow and endolymphatic potential. Furthermore, since many of the venous vessels in the scala tympani have little or no bony covering and are essentially exposed to the perilymphatic space, the venous system is a route of entry for the cells participating in the inner ear inflammatory process. [14]

Another interesting point is that the blood leaves the brain by using the back propulsion of the residual arterial pressure (vis a tergo), complemented by antero-

grade respiratory mechanisms (vis a fronte). The latter consist of the thoracic pump increased venous outflow during inspiration: the increase of negative thoracic pressure improves the aspiration of blood toward the right atrium. In addition to vis a tergo and vis a fronte, postural mechanisms play a fundamental role in ensuring a correct cerebral venous return.

The pattern of cerebral venous drainage changes, even under physiological conditions, is thus depending on the body position. In the prone or supine position, the outflow through the IJVs is favoured, whereas passing to the upright position transfers most of the encephalic drainage to the vertebral veins. [15]

In recent years, together with gradual improvement of Duplex machines, interest has been gained in searching anatomical diagnostic areas that appear both critical and challenging, for the operator and the apparatus that is being employed. The vascular anatomy of the cochlea is the most unusual and probably the most difficult to evaluate. The blood flow is segmentally, centrifugally, and centripetally arranged, with many spirally perpendicular vessels shunted in, suggesting good possibilities for variations of circulation. There is a pronounced apical simplification of the vascular pattern probably more than corresponding to the decreasing volume of the turns. The blood supply of the scala vestibuli is mainly arterial; that of the scala media is capillary or by-pass, and that of the scala tympani is venous. For this last reason, and more recently, the Duplex examination is carried out also in an upright sitting position, always kept comfortable for the neck, so to register the difference of the venous outflow according to postural pressure and different breathing activity.

The cochlear artery, often correlated with severe sudden deafness [16,17], appears one of the most difficult vascular exams to carry out. Moreover, this exam isn't easy to transform into a standard path, like for example the most common Duplex exam of the carotid arteries, because the anatomical access is extremely difficult and varies from one patient to another, or even gender since women generally have a smaller structure and window access to the area.The two sides appear very much like a stereophonic Hi-Fi apparatus and so both should register similar bloodstream haemodynamic flow. An important predominance of one side upon the other clearly is abnormal.

The most frequent abnormalities detected with the internal jugular veins along their extra-cranial way. In case of a pathologically slow jugular outflow and secondary venous hypertension [18], other veins have to increase their normal activity of venous drainage and Duplex is the only possible exam, up till now, that allows imaging in lying and sitting positions and also requires patient interaction. The vertebral veins appear to be among those that increase, as far as it is anatomically possible, the venous drainage. Not rarely, also the vertebral outflow appears insufficient and, consequently, venous hypertension can be present also in this segment.

It is now being demonstrated that venous outflow problems are present in several progressive neurologic diseases. Symptoms may vary in percentages but, those regarding postural and/or listening problems seem to be always more frequent in all the diseases. [4]

The echo-colour Doppler (ECD) is the ideal tool for dynamic assessment of both cerebral arterial inflow and venous outflow. In our patients ECD indicated dynamic abnormalities of blood venous cerebro-spinal drainage quite exclusively in Meniere Disease and arterial alterations in no-Men group and normal cerebro-cephalic pattern in BPPV.

On the basis of our results we can suggest that blood outflow could play a pathogenetic role in Meniere Disease [19] while in no-Meniere Disease cochlea-vestibular damage may be mainly sustained by a reduced blood inflow. Substantial normalities of ECD in BPPV confirm that BPPV is a vestibular dysfunction and not a lesion of he inner ear, at least in the majority of the cases.

To the best of the authors' knowledge, the association between Meniere Disease and CCSVI has never been published.

CCSVI might explain the anatomical background which provides a predisposing factor for cochlea-vestibular diseases, in general, and Meniere Disease, particularly. ECD if aimed to detect specific blood flow abnormalities is a specific tool for the pathogenetic differential diagnosis in cochlea-vestibular disorders

Further studies in larger groups of patients are needed to investigate the exact mechanisms and correlation between inner ear diseases and Cerebrospinal Artero-Venous flow abnormalities.

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ScienceMED, vol. 4, 1.2013, 17-19, Bologna (Italy)

Diagnostic and rehabilitation of vestibular disorders with using of telemedicine tools

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Summary

Vestibular disorders are more and more common. Numerous patients are subjected to surgery and after that a rehabilitation period can be carried out in an outpatient clinic. Centers of Hearing and Speech "Medincus" are connected via telemedical network with a higher reference center and offer telerehabilitation services. In the study we analyze results of patients with vestibular disorders and present their diagnostics and treatment. 300 patients were examined on August 2012 – December 2012. We found 120 patients (40%) with BPPV, 99 (23%) unilateral labyrinth failure, 4 (1,3%) bilateral labyrinth failure. In the study different methods of rehabilitation and treatment were applied as well as confirmation from other specialist was included. Concluding, there is an urgent need to increase more specialized local diagnostic and rehabilitation centers. Application of special tools used in rehabilitation allow to obtain better results and patients' satisfaction after treatment.

Introduction

Vertigo and dizziness are the frequent diagnostic and therapeutic problem that general practitioners such as laryngologists or neurologists have to deal with [1]. In some cases vertigo may occur in the postoperative period. Then a consultation, especially in cases of cochlear implantation should be performed [2]. Telemedical network connects 20 centers in Poland and 1 abroad in Odessa, Ukraine. In that centers we perform teleconsultations, telerehabilitation, telediagnostics and telefitting. The teleaudiology, including telefitting and telerehabilitation, is an innovative method that uses a system for remote rehabilitation and fitting of speech processors of cochlear implantees [2,3]. The telefitting and telerehabilitation are crucial for the patients after Partial Deafness Treatment and in aging population [4,5]. The equilibrium is an essential function and

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cannot be entrusted to a single organ or apparatus, but it requires an entire system, a set of communicating structures and processes [6]. The aims of the balance system are: visual control of the environment, posture and motion control, spatial –temporal orientation, autonomic reflexes regulation, psychological well being [7,8].

Material and Methods

In this paper we present results of assessment and rehabilitation of 300 patients who were treated at the West Pomeranian Center of Hearing and Speech "Medincus", Szczecin, Poland. They reported vestibular disorders in high reference clinic or at other clinics. Patients age ranged from 9 to 73 years old. The majority of the patients were females 187 (males – 113 subjects). Every patient was tested with the VNG test and computerized dynamic posturography [9,10]. We were looking for: any slowness or inaccuracies in an ability to follow visual targets which may indicate a central or neurological problem or possibly a problem in the pathway connecting the vestibular system to the brain (ocular mobility). We were looking for spontaneous nystagmus, positional nystagmus. Caloric tests and computerized dynamic posturography were performed in all patients.

Results

In the group of 300 patients we found 120 patients suffering from BPPV, 99 patients with unilateral vestibular loss and 4 persons with bilateral vestibular loss, 12 patients suffered from migraine, 20 patients with psychological basic and 40 with normal results.

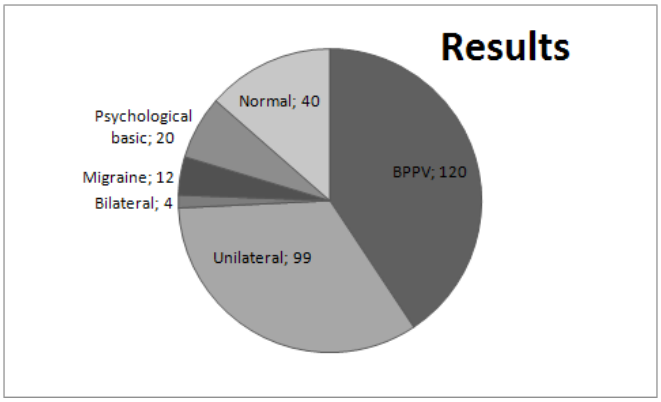

Fig. 1. Vestibular disorders among patients selected for the study

Patients with BPPV had adequate treatment and got rid of vertigo symptoms. Patients with unilateral or bilateral loss (n=103) had vestibular rehabilitation therapy. After the rehabilitation we measured if the rehabilitation reduced symptoms of dizziness, improved postural and gaze stability, and independence. 89 patients claimed that vestibular rehabilitation reduced symptoms of dizziness, 101 patients confirmed that

rehabilitation improved postural and gaze stability, 101 patients said that rehabilitation improved their independence. All responses found confirmation in an objective research.

Conclusions

To sum up there is a need for more specialized local diagnostic and rehabilitation centers. Due to some complicated cases of patients, direct and fast contact with a high reference center should be obligatory to enhance good clinical results. The complicated cases are often in cases of patients with congenital malformations, not only with vestibular disorders [11]. Use of specialized rehabilitation tools allows us to obtain better results and patients satisfaction after treatment.

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ScienceMED, vol. 4, 1.2013, 21-23, Bologna (Italy)

Vestibular aspects in cochlear implant procedure

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Summary

Cochlear implantation procedures are nowadays accepted surgical procedures dedicated to patients with deafness. During recent years indications were extended and we can observe long-term results in patients after Partial Deafness Treatment (PDT). Aim of the study was to analyze possible vestibular complications that may occur during surgery and vestibular disorders among cochlear implanted patients. In a material of the Institute of Physiology and Pathology of Hearing there is 3994 cochlear implant patients. Vestibular failures and surgical complications are not common in centers that perform large number of otosurgeries including numerous cochlear implantations per year. Vestibular problems may be mainly caused by either insertion of the electrode to semicircular canals or mechanical motional abnormality of the ossicles. Vestibular system assessment, applying a battery of tests dedicated to cochlear implantees, is recommended.

Introduction

The first cochlear implantation in Poland was performed in 1992 [1]. Assessment procedure always is focused on hearing tests and possibilities of stimulation of the cochlear part of the n. VIII with an electrode. During last years of previous century and beginning of the new century some centers have begun to add acoustic stimulation to cochlear implants. The first classification of patients selected to that procedure was announced in 2009 during 10th European Symposium of Cochlear Implantation (Fig. 1) [2,3]. Depending on a hospital we can observe increase of number of studies based on Head Impulse Test (HIT) or Vestibular Evoked Myogenic Potentials (VEMP) [4,5,6]. In cases of similar hearing and anatomical conditions vestibular evaluation could be

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one of decisive factors in the choice of the operated ear. The aim of the study was to detect vestibular disorders after cochlear implantation.

Materials and Methods

By August 2013, 3913 cochlear implantations have been performed in the Institute of Physiology and Pathology of Hearing in Warsaw and Kajetany. There was no routine vestibular assessment in these cases before surgery. One of the important factors is the age of patients since in children population it is difficult to obtain reliable results [7]. Recently there are more and more examination performed, especially in genetic disorders and congenital malformations [8]. The other group consisted of adults who were selected for Partial Deafness Treatment. In these patients it was important to assess vestibular functions in cases where there was a need for ear choice while other factors were comparable. In an assessment there were included caloric tests and the VNG. If any patient complained, additional CT scans were analyzed during the follow-up period.

Results

We observed 46 patients with periodical vertigo which disappeared within 2-3 days after surgery. Mainly it was correlated with longer than usual time of surgery. In 2 adults we had cochlear implant electrodes introduced in the lateral semicircular canal. One was diagnosed during the surgery with the Cone Beam CT – Xoran [9]. Then immediate reinsertion was performed. The second case was performed 2 days after initial surgery. Both surgeries were performed using cochleostomy approach and perimodiolar electrodes.

Conclusions

We recommend to put special attention in vestibular disorders before cochlear implantation in patients with: Usher Syndrome (especially IB), after in utero rubella exposure, Waardenburg disease, Jervell-Nielsen syndrome, Pendred syndrome, Goldenhar syndrome, CHARGE. There is a great advantage of the round window approach in comparison to cochleostomy in preventing vestibular disorders. Some factors are crucial in that question. The first is bony dust particles after drilling when they move to semicircular canals. The vibration during drilling could be sufficient to dislodge several otoconia into the labyrinth. Another, however no common cause could be dislodging of an otolith because of the electric stimulation that occurs during initial fitting [10]. It is very important to conduct profound analysis of a vestibular system in progressive hearing loss with deep insertion of electrode [11].

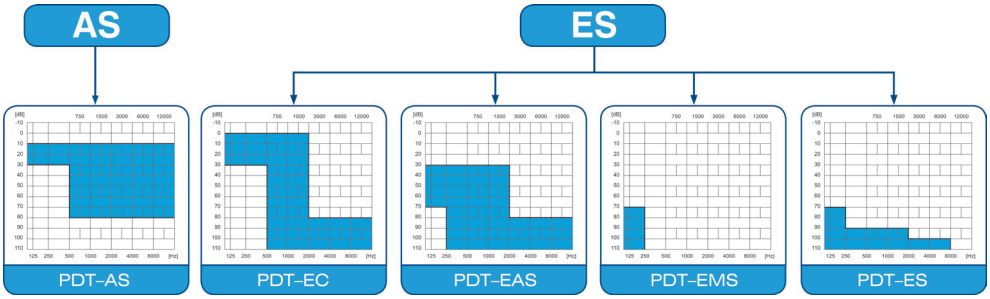

Fig.1 Partial Deafness Treatment classification

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ScienceMED, vol. 4, 1.2013, 25-27, Bologna (Italy)

Mechanical bridging to recovery after heart transplantation

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Heart transplantation is becoming increasingly difficult, mainly due to a tremendous donor shortage. As a consequence, much more borderline donor organs are accepted, and the risk allograft dysfunction rises. Eventually, patients suffer primary graft failure with low cardiac output, hypotension, and increased filling pressures. During the first 30 days after surgery, primary graft failure is the most frequent cause of death according to the ISHLT data (www.ishlt.org). The reasons for primary graft failure include long ischemic time with inadequate organ preservation, use of marginal donor organs, old age, high-dose inotropic support, size mismatch and pulmonary hypertension. Early death rates are high, and long-term survival is clearly inferior.

Treatment strategies of primary graft failure consist of inotropic drug therapy including levosimendan, mechanical support, and retransplantation. As drug therapy usually fails and retransplantation is nearly impossible (in most countries) and also yields unfavorable results, various kinds of mechanical support represent the therapy of choice. If the clinical situation seems to be borderline with a moderately impaired global pump function, the placement of an intra-aortic balloon pump (IABP) can be considered. There is hardly any contra-indication apart from severe peripheral occlusive arterial disease. However, the effectiveness with regard to the cardiocirculatory stabilization is limited and a recent study, where the IABP was tested in shock situations after myocardial infarction showed no benefit.

Sufficient short-term mechanical support can be provided with the implantation of ventricular assist systems (VAD) and extracorporeal membrane oxygenation (ECMO). In case of global heart failure, biventricular support is necessary, which can be provided with several devices. The Abiomed BVS 5000 is a bed-side full automated system which was largely used in the past, but is now no longer available. The idea of the company for a bed-side transition to a left-ventricular or biventricular VAD was not accepted by the community for various reasons. Instead, paracorporeal pneumatic VADs such as the Thoratec PVAD or the BerlinHeart Excor remained the standard, supplemented by the CardioWest total artifical heart. More recently and with the exchange of old-fashioned roller pumps with modern centrifugal pumps, extracorporeal solutions with Rotaflow (Maquet) or the CentriMag (Levitronix) pumps

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were implemented as left and right ventricular assist device. They were connected to short-term cannulas or to cannulas of the paracorporeal devices allowing longer-term support and a later switch to the respective pump chambers. The reported literature is sparse and the results are disappointing with survival rates of about 30 % after a support interval of 1-2 weeks.

	Patients	System	Duration	Survival
Jaggers	1	Thoratec	18 days	(100 %)
Albes	1	BerlinHeart	7 days	(100 %)
Kavarana (2003) (1)	18	Abiomed RVAD=11 LVAD=4 BiVAD=3	1-40 days	28 %
Arribas	1	Medos	7 days	(100 %)
Santise	2	Levitronix	2 / 7 days	(100 %)
Shuhaiber (2008) (2)	6	Levitronix	7-14 days	50 %

Tab. 1: Ventricular assist devices for primary graft failure

The alternative is to use venoarterial ECMO. There are several systems on the market with the Cardiohelp (Maquet) being the most sophisticated one. Cannulation can be performed centrally using the cannulas of the heart-lung machine, or peripherally via the femoral vessels. Central cannulation is highly effective, but poses a significant risk for infection. Peripheral cannulation offers the advantages of a closed chest, less bleeding, and a lower risk of infection. Side effects include a hazard of leg ischemia and only partial unloading of the heart. There is little information in the literature too, but the outcome is much better with survival rates of 60-70 %.

We share the same good results in our institution. The value of an additional or general left atrial unloading is unclear.

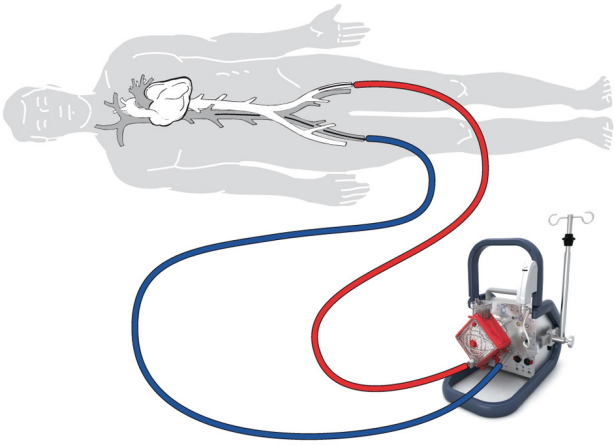

Fig. 1: Peripheral ECMO cannulation

	Patients	Support	Weaned	Survival
Taghavi (2004) (3)	28 (RV failure)	ECMO=13 RVAD =15	10 (77 %) 2 (13 %)	7 (54 %) 1 (7 %) (graft survival)
Leprince (2005) (4)	14	ECMO: Peripheral=13 Central=1	9/12 (75 %)	8 (66 %)
Marasco (2010) (5)	39	ECMO: Peripheral=26 Central=16	34 (87 %)	29 (74 %)
Listijono (2011) (6)	17	ECMO: Peripheral=17		14 (83 %)
Bittner (2011) (7)	14	ECMO Peripheral=14	9/14 (64 %)	6 (43 %)
Mihaljevic (2012) (8)	53	ECMO=43 RVAD=6 BiVAD=4	19 (36 %)	-

Tab. 2: ECMO for primary graft failure

In summary, early ECMO implantation is nowadays preferred in case of primary graft failure. Central cannulation allows higher flows and better ventricular unloading, peripheral cannulation has a lower risk of mediastinitis.

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ScienceMED, vol. 4, 1.2013, 29-34, Bologna (Italy)

Replacement of Ascending Aorta with Bentall DeBono Technique

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Abstract

This is a retrospective observation study after identification of all patient cohorts who underwent aorta replacement in patients with Acute Aortic Dissection (AAD) in our Institution since May 1994 to November 2008. The population was predominantly male (16=84.2%) and three female (15.78%), mean of age 50.2 years and hypertension was the most significant factor. The operating procedures were Bentall De Bono and St. Jude and Carbomedic composite valve replacement grafts (CVGR), used indistinctively. Hospital mortality rate was 15.78% (three patients), the freedom from reoperation at 15 years was 89.48% and three patients died during the follow-up period, 68.4% long-term survival. Our results confirm that Bental De bono procedure is still an excellent choice for AAD.

Keywords: *AAD, Bentall DeBono procedure*.

History

The first described aortic aneurysm is found in Ebers Papyrus (1552 BC), discovered by Ewin Smith in Luxor 1862. Each Galen (II Century AD) and Vesalius (XVI Century) had given some information about arterial dissection, but was Sennertus who, in 1650, made the first description of the dissection aortic process. A century later, in 1761 Morgagni described a case of broken aortic dissection (referring to the case of King George II of England) based on the findings of the autopsy that Nicholls conducted a year before, which corresponded to what now is known as aortic dissection, a name which, in turn, was given by Maunoir in 1802.

The first reports on aortic root repair were made by Hufnagel (1962) and Morris (1963); in same year, Starr reported an ascending aorta replacement plus a mechanic prosthesis in the aortic position. Five years later, Bentall and Bonno reported (1968) the total replacement of the aortic root with a valve conduit (composite root replacement).

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Introduction

Acute aortic dissection is a very serious life-threatening situation and despite debates about the etiology, there is no question that hypertension plays the most significant role. It is initially the rupture of the inner lining of the aorta, creating a new pathway where the blood penetrates and separates the wall layers and depending on how far the dissection goes, it would appear signs of presentation corresponding to the organs involved; the more organs involved, more worse the prognosis is. The risk of complete rupture of the wall of the aorta remains high and if it is consumed, its mean the end of the dissecting process and, consequently, imminent death of the patient.

We witness and also are protagonists of the decreasing mortality in all centers where different types of surgery to correct this problem were performed, notwithstanding it still represents a dangerous challenge due to AAD lethal condition and even though obtaining the optimal care at the best hospitals of the world. Since the introduction of ascending aorta replacement with composite graft by Bentall and De Bono in 1968, life expectancy for patients with different types of aortic root problems has significantly increased.

We all know the crude mortality rate in its natural evolution and the urgency of the surgery; then, when talking about AAD, we talk about an evolution time of less than two weeks; beyond that period of time, we are talking about chronicity, we also talk about other behavior and strategies that will not be discussed this time.

There are three main classification for AAD: DeBakey (1965) describing 3 types (I, II, III), Daily (1970) describing 2 types (A and B), and Crawford (1986) who have 4 types (I, II, III, IV), but is Daily (Stanford) the one widely accepted by most authors around the world. As far as we are concerned, we confess our preference for the first one, but the discussion of this topic shall take place in another occasion.

It happens more in men than in women, at a rate of 2:1 and 5:1 (Shennan-Hirst-DeBakey) and its frequency, in accordance with large studies, is placed between 5 to 10/million/year (Rahbeck-Sorensen HR, Olsen H and wheat) and 20/million/year (Pate et al).

Material and methods

We present our experience in the replacement of aortic root by Bentall DeBono technique in nineteen (19) patients performed for Acute Aortic Dissection (AAD) type A or type I and II Debakey. Sixteen patients were male and three (3) female, in ages comprising 36 to 62 years. Diabetes Mellitus was present in eight patients, obesity in five, five smokers and seven with dyslipidemia. All of them with hypertension and all complaining of sudden stabbing/burning intense chest pain; three patients with acute myocardial infarction in progress, seven with hypertensive crisis and one with calf necrosis of right lower limb. Likewise, eighteen of them presented a variable grade of renal failure (in fourteen patients creatinine above 1.5 mg/dl), including three with anuria requiring repeated post-surgery dialysis. Only two cases did not present severe aortic failure (mild-moderate), cases where a supra coronary tube implant and aortic valve plasty were necessary; three (3) cases were associated to CABG, all saphenous to right coronary artery. The diagnosis was confirmed by ETE in all cases, thoraco-abdominal TAC in seven cases and catheterization in 14 patients (in 45 years old patient or more).

Surgery

The surgical technique consisted of standard sternotomy, CPB by femoral cannulation and double drainage cannula in right atrium (one case with femoral-femoral cannulation), hypothermia not lower than 30˚C (32˚C in general). The myocardial protection was obtained by antegrade and retrograde administration of cold haematic cardioplegia and topical cooling with 4˚C saline solution. A Teflon circular reinforcement was always placed in distal anastomosis. The ECC time fluctuated between 126 minutes to 364 minutes and the clamping time was 104 minutes to 130 minutes. Because there were not cases with supraaortic branches impairment, it was not necessary to reimplant them, also not necessary to use brain protection as well. A St. Jude and Carbomedics composite grafts were used indistinctively.

Three (3) died in operating room (OR): two (2) by massive pulmonary hemorrhage and the other by severe coagulopathy. In ICU, two presented serious pleural effusion that needed thoracentesis; one (1) was re-operated due to cardiac tamponade; three patients (3) with low cardiac output, requiring high inotropic doses and the other one requiring daily debridement and, in ambulatory manner, in the calf area for two months. The early mortality rate was 15.78%. (Table I).

TABLE I – COMPLICATIONS

Hemorrhage + mortality	3
Low Cardiac Output	3
Post-operative dialysis	3
Pleural effusion	2
Tamponade + Reintervention	1

Follow-Up

In the follow-up period of 54 to 183 months, one patient with aortic valve replacement two months later due to aortic valve plasty failure; one patient with bypass (Gore Tex) from left common carotid artery to left axillar artery due to subclavian thrombosis 4 years later; we should say that duplex and angiotac made prior to bypass revealed no dissection in any supraaortic vessel. Other required Stent in saphenous graft 5 years later; other patient with annoying chest wall pain complain controlled with Pregabaline, other with endurable left hemiparesis, one patient with recurrent atrial fibrillation and other with mild-moderate aortic valve insufficiency. Two patients with a mild mitral insufficiency and trivial tricuspid insufficiency. Five patients keep creatinine high levels (table II). Three (3) patients died: one (1) for stroke at 9 months after surgery and two others three and seven years later for unknown causes (table III). The rest of patients (68.4 %) are asymptomatic and following their normal rhythm of life, according to annual consultation. (Fig 1)

TABLE II – Follow up

Creatinine 1.3 – 1.6 mg/dl	5	Stent Saphenous Graft	1
Death	3	Mild-moderate aortic Valve Insufficiency	1
Mild mitral valve insufficiency	2	Calf Necrosis Right Limb	1
Trivial tricuspid valve insufficiency	2	Chronic Chest Wall Pain	1
Redo + Aortic Valve Prosthesis	1	Mild left Hemiparesis	1
Carotid Axillar Bypass	1	Recurrent Atrial Fibrillation	1

TABLE III – CAUSE OF DEATH

Hemorrhage	3
Unknown	2
Stroke	1

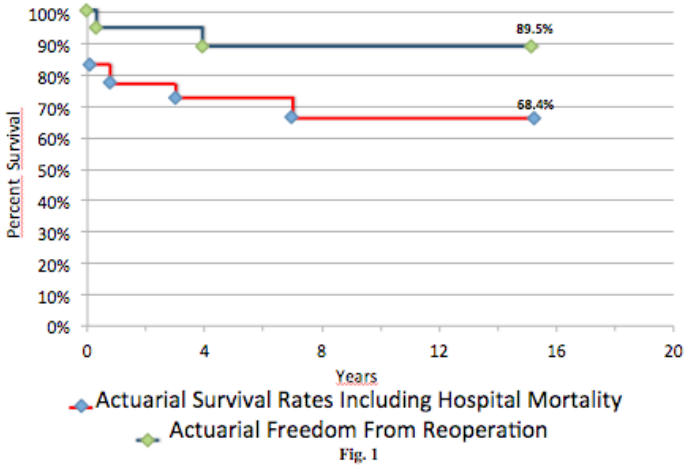

Fig. 1

Comments

According to researches, AAD frequency should be between 50-200 cases per year taking into account our general population. The present series demonstrates that we do not have the number of patients that would correspond per year and there are only two ways to explain: first, by the limitations of hospitals in the public health system of our country and the economic limitations of many of the affected who cannot afford private medical services. Second, this rule does not apply in Dominican Republic. Not knowing exactly the true frequency of AAD in our population, we accept as good and valid what is handled in the literature. In the mean time, we wait for mandatory autopsies of all deaths and then we would know.

Despite the small number we present, we wish to be as accurate as possible and highlight various data, which in our opinion, are striking: both type I (10 cases) and type II (9 cases) under DeBakey classification are practically equal in our series (60% and 10-15% respectively according to literature); the rate of acute myocardial infarction was 15.78% against 1-2% of literature and none of the 19 AAD cases we found supraaortic vessel damage. Finally, we draw your attention to the discovery (post mortem) of two undiagnosed giant persistent ductus arteriosus directly related to the cause of death in two deceased patients in OR, there were no similar cases in the literature.

In addition, it is important to emphasize that we have no one prosthetic endocarditis, no reoperation because of graft related complications and no anticoagulant related hemorrhage in seven patients with mechanic valve prosthesis. Also, we found

no cases of connective tissue disorders, history of trauma, pregnancy, previous heart surgery, congenital heart diseases, etc. So, we have no doubts that we would see how this change as cases increase.

Conclusion

1. Due to the low morbi-mortality range of our still small casuistry, we ratify that Bentall De Bono technique is a safe and excellent choice for AAD type I and II Debakey or type A Stanford and represent low operative risk and optimal long-term outcome.

2. We believe that we have to improve all diagnostic procedures in State hospitals and make more effective moving of patients affected with AAD in our country.

3. Surgery in ascending aorta, in general, does not guarantee freedom from future aortic events, but it has been in our series so far.

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ScienceMED, vol. 4, 1.2013, 35-41, Bologna (Italy)

Intramyocardial Implantation of Stem Cells in Combination with CABG in AMI with Severe Ventricular Dysfunction. First Cases in Dominican Republic

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Abstract

Objetive: To demonstrate the feasibility of stem cells (SC) implant into the myocardium associated with coronary artery bypass grafting (CABG) in our country, also to demonstrate the effectiveness of SC in cases of myocardial infarction with severe ventricular malfunction.

Methods: An aorto-coronary bypass surgery plus intramyocardial bone marrow stem cells implant was performed in two males with severe ventricular malfunction post-infarction. There were no intraoperative and postoperative complications. During a follow-up period of 65 to 84 months, we have no morbid events at all and an unquestionable improvement of patients' clinical condition. The post surgery Sestamibi tests reveal a clear increase of myocardial perfusion with regards to prior surgery tests, demonstrating adequate cardiac muscle regeneration.

We conclude that our results reproduce the findings described in the literature as evidence of cardiac muscle regeneration.

Keywords: stem cells, CABG, myocardial infarction, severe ventricular malfunction, Sestamibi, muscle regeneration.

Introduction

Since the Russian histologist Alexander Maxímov proposed the term Stem Cells (SC) for hematopoietic cells in 1908 at the Congress of Hematologic Society in Berlin to define the existence of these cells, many things have occurred from then, so a new

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medical specialty so-called Regenerative Medicine has emerged base on the study of SC capacity to modify and turn themselves into different types of cells and tissues, whose objective is the bioengineering production of tissues and functional organs to replace natural damaged organs. The SC is undoubtedly one of the more remarkable medical discoveries of the end of the 20th century.

It was in 1963 when the scientists began to recognize SC potential when Till J. and McCalloch E. demonstrated the presence of self-renewing cells in the bone marrow of mice. In 1967 Cavins J. performed the first peripheral blood stem cells (PBSC) transplantation in dogs and Shpall performed in 1993 the first PBSCT in humans. Then, Cossu G. published in 1998 a study showing myocardial regeneration post SC implant in mice as an alternative to heart transplantation. Chachques JC performed in France (2002) the first SC CD34+ implant in open heart surgery in combination with CABG. This fact meant a milestone in such a way that today are countless works regarding the combination of SC with CABG perform all over the world.

Two types of SC are known: embryonic stem cells (ESC) and adult stem cells (ASC). The ESC only exists in the early stages of human development and is branched from the inner cell mass of the blastula; they are capable of producing any kind of cell of embryonic and extraembryonic tissues. The ASC is present in fetuses at development, newborn, children in general and all adult individuals. They are so pluripotent as the ESC and are present in all tissues but especially abundant in fatty tissue, bone marrow, blood, skin, muscle, hair, therefore, they are easy to get.

It is not yet known how SC does it, but we know they produce angiogenesis and myogenesis, so therefore in the infarcted heart improves ischemia and improves the myocardium contraction. As a result, the remodeling stops and over the time the ventricle tends regaining its original shape and restoring ventricular function. Not everyone is convinced of the effectiveness and benefits of SC, but we all know that are many expectations with cell regeneration therapy, all hopeful.

Material and Methods

From August 25, 2006 to December 10, 2008 nine surgeries were performed in two Centers, all males, aged between 51 to 60 years. All with hypertension, six obese, five diabetic, three dyslipidemic and three smokers. One patient died due to severe hemorraghae at 5th day in ICU, another died due to massive AMI, at 32 days, probably due to treatment drop once discharged from hospital. The seven remaining cases, five were unable to perform Sestamibi serial tests, but we can assure they are doing well; therefore, we present two cases.

Inclusion/Exclusion Criteria

Patients qualifying for this procedure are those with ischemic heart disease, with AMI history, akinetic or dyskinetic scars, and no CABG possibility; EF $\leq$ 40; functional class $\geq$ II and non-ischemic dilated cardiomiopathy. Furthermore, we excluded patients with a history of tachycardia or ventricular fibrillation, implanted defibrillator; AMI < 4 weeks; neoplasias; pregnancy and infectious diseases such as HIV and Hp.

Case I

54 years old
HTA
Dm-II
antero-septal AMI August/99 - **Fig 1**
EF: 22%
Dyspnea at rest
Weight loss
Malleolar edema
Intolerance to decubitus

Case 2

54 years old
HTA
Dm-I
inferior-lateral apical AMI, Dec/07 - **Fig 2**
EF: 26%
Angor at minimum effort
Obese
Smoking
Dyslipidemia

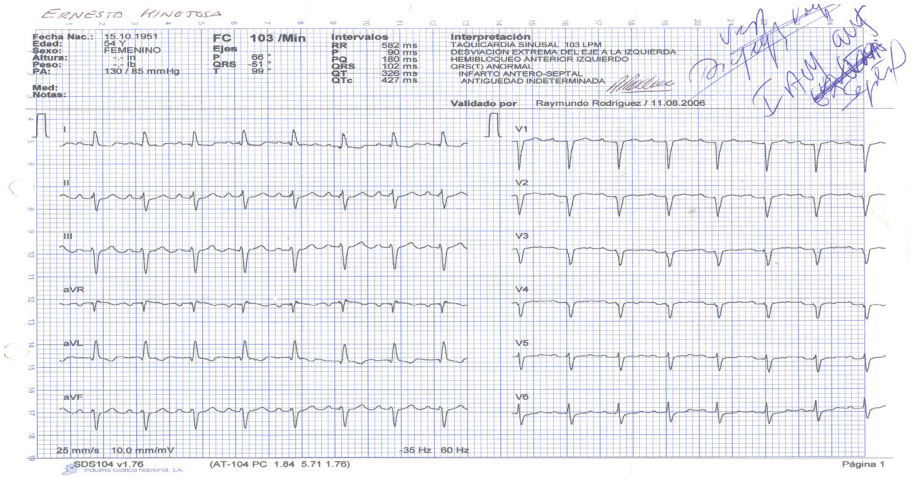

Fig. 1 - EKG case 1

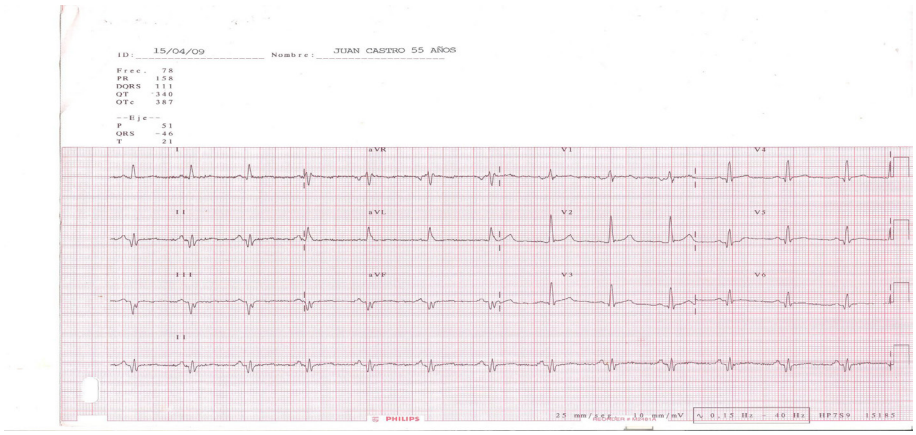

Fig. 2 - EKG case

Preoperative treatment

- Nitrates-Ivabradine**
- ACEI-Trimetazidine
- Carvedilol/Nebibolol/bisoprolol**
- Furosemide
- Spironolactone
- Antiplatelet (suspended 1 month
- Statins: higher doses
- Amiodarone (initiated 1 month before procedure)
- Chemotactics for cell stimulation: GCSF in daily doses every 12 hrs during 6 days prior to surgery) before procedure)

***if we use Ivabradine, we do not use Betablockers and viceversa*

Surgery

Just before starting the surgery, the bone marrow is removed from one of the two iliac crests; the material is taken to the lab to separate and select SC CD34+. In the first case (August 2006), off pump technique (OPCAB) was fixed to perform four aortocoronary bypasses: LIMA-Dca, saphenous-D1, M1 and M2. Wide endarterectomy in Dca and M1. Then, 12 millions of CD34+ were implanted around the infarcted area. In case two, we performed (March 2008) the same general procedure, three coronary artery bypass: LIMA-Dca, saphenus-Pda and M1, implanting 18 million CD34+ around the infarcted area; one shot through each saphenous graft is always done.

Results

There were no complications in the intraoperative or postoperative and both patients were discharged the sixth and fifth day of evolution, respectively. Serial echocardiograms in follow-up reviews showed continuing improvement of cardiac function (**Fig 3**). With regards to prior test, post surgery Sestamibi tests show a clear increase of myocardial perfusion, demonstrating adequate cardiac muscle regeneration after procedure. (**Fig. 4, 5, 6, 7**).

During 65-84 months follow-up period we have not found any morbid events and the final results show unquestionable improvement of patients clinical condition.

POSTOPERATIVE ECHOCARDIOGRAPHIC EVALUATION

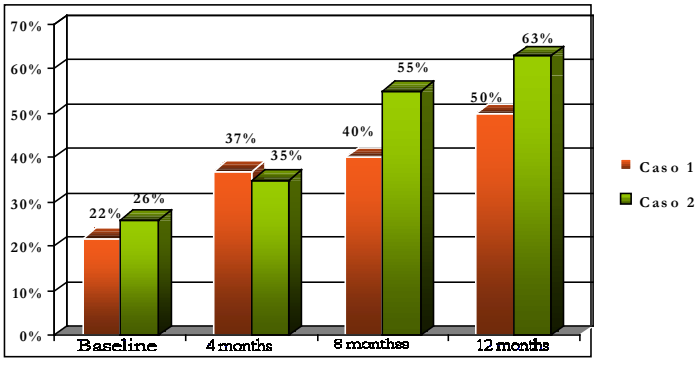

Fig. 3 - 1st. year Ejection Fraction follow up

Case 1

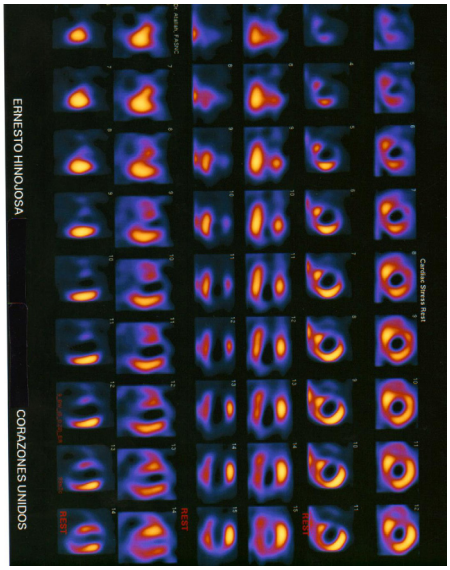

Fig. 4-July 2006

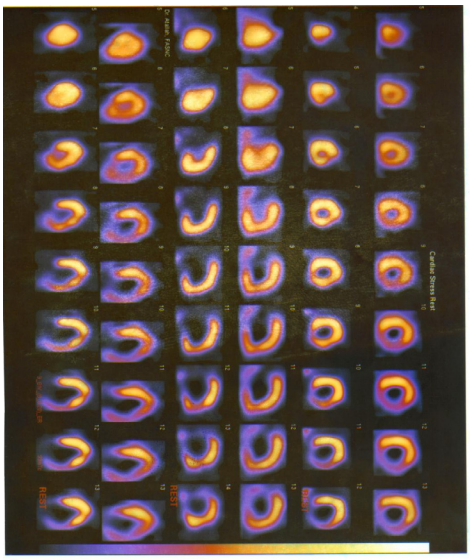

Fig. 5- December 2010

Case 2

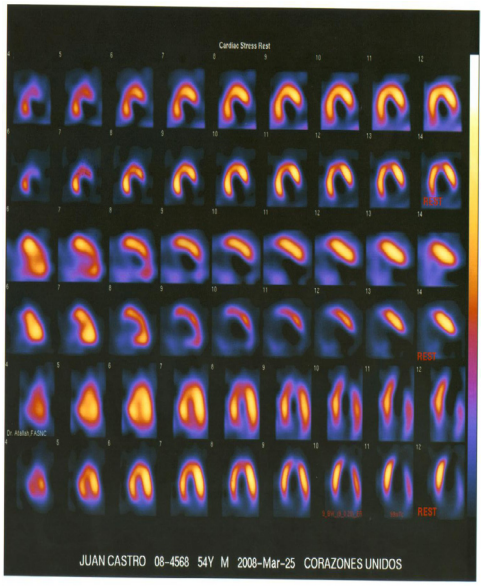

Fig. 6 - March 2008

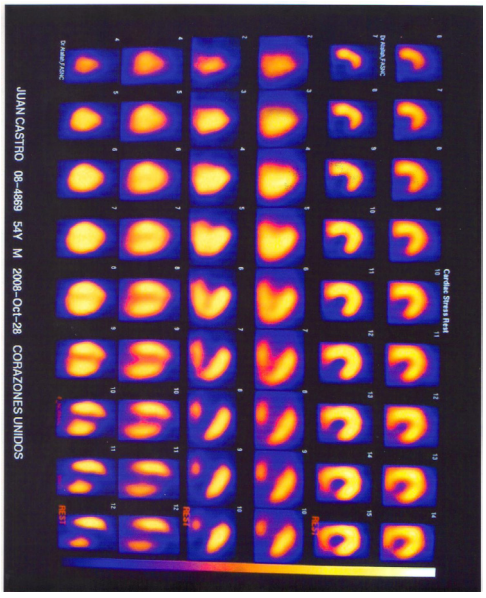

Fig. 7 - October 2008

Comments

The heart failure demands a comprehensive and multidisciplinary management involving the cooperation of others specialties, many and different drugs, ventricular restoration surgeries (defibrillators, resynchronizers, VAD, SAVE operation, Jatene-Dor operation, Stem cells therapy, etc.), surgeries for ventricle replacement (bridge to destiny, TAH, HT), etc.

In USA the heart failure at its different stages consumes an annual budget ranging between 35,000 to 40,000 million dollars; the annual budget is more or less similar in the EEC. We can imagine how much spend the Chinese State with 1.5 billion inhabitants and India with 1.2 billion inhabitants. So, the global budget is not only unimaginable, but also unsustainable.

Cell regeneration therapy is a novel and attractive therapeutic alternative that would change forever the meaning of catastrophic diseases that drag huge sums of money from State budget; also it would significantly reduce a health public system already overwhelmed. Cell therapy is an exciting and yet little explored field of modern medicine; therefore, we still cannot assure that SC are the definitive cure for serious diseases; but we are completely sure that we are not very far from that goal.

Looking at the results of works in sport medicine, cardiovascular surgery, orthopedics, oncology, hematology, rheumatology, dermatology, etc., which show the indisputable benefits of SC in terms of regenerating damaged tissues, it means the reduction of human suffering and thereby a considerable improvement of quality of life (QOL) and average of span of life. We believe that the "crippling" chronicity of heart failure is seriously threatened.

While the SC represents a hopeful future, there still exists opposition in the 5 continents and generates many controversies, especially when they refer to embryonic stem cells. They argue ethical, social, religious, economic, political and legal reasons and more. There are even those who oppose SC because they do not believe in its effectiveness; others do nothing, just wait. In any way, should not have opposition to an autologous tissue implant due to the fact that the implant is SC.

We believe it is our duty to reaffirm that any autologous tissue implant is absolutely harmless, so there is no controversy in hair implant, no controversy in saphenous implant on myocardial revascularization and no controversy in skin implant in lower limb ulcer refractory to treatment. It seems necessary to recall that United States FDA confirmed in 1997 that the autologous tissue implants do not require any regulation and… that is a right answer for the dilemma.

Conclusion

- The CABG combination with intramyocardial implantation of stem cells from bone marrow reproduce the findings described in the literature as evidence of cardiac regeneration.
- It is a feasible technique in our country and shows effectiveness in patients with severe systolic dysfunction.
- Based in the results obtained in the so far first and only cases in the Dominican Republic of intramyocardial implantation of stem cells combined with CABG, contribute to the further implementation of this technique.

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ScienceMED, vol. 4, 1.2013, 43-48, Bologna (Italy)

Clinical and echocardiographic results with a new three-dimensional tricuspid ring

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Abstract

Introduction: We present our initial experience with the new three-dimensional ring Carpentier-Edwards-Physio-Tricuspid,(CEPhT). Methods: We used this ring in 64 patients. The indications for tricuspid annuloplasty (TA) were the presence of a severe tricuspid regurgitation (TR) (39%) or a slight or moderate TR associated with significant annular dilatation (61%). The expected mortality estimated with EuroScore I and II was 10.05% and 6.23% respectively. Results: The immediate postoperative mortality was 4.6%. The ring implant was technically simple and there were no perioperative complications. Survival at 16 months was 90.6%. The echocardiographic study showed freedom from recurrent moderate-severe TR in 92% of patients. Conclusions: The new three-dimensional tricuspid ring corrects TR effectively and provides good short-term clinical and echocardiographic results.

Introduction

Functional tricuspid regurgitation (TR) is common in patients with left valvular pathologies.

The most common mechanism of TR is type I Carpentier's functional classification (anular dilatation)[1]. The dilatation of the tricuspid annulus does not affect its four segments to the same degree. Annular dilatation affects mainly in anterior/posterior segment.

This functional TR is most of the time amenable to surgical reconstructive techniques (suture or prosthetic annuloplasty). Tricuspid annuloplasty (TA) with a ring is the most widespread repair technique due to its high efficiency. Several clinical series have shown the superiority of prosthetic remodeling annuloplasty over other surgical techniques[1, 2-4].

We present our initial experience with the new three-dimensional ring Carpentier-Edwards Physio Tricuspid (CEPhT) in patients with significant functional TR who underwent tricuspid valve repair with this prosthesis in combination with left-sided

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valvular surgery or other concomitant surgical procedures, patients with moderate or severe TR or patients with mild to moderate TR and severe annular dilatation (>40mm). Recent clinical data suggests that moderate to severe TR remains present in 10% of patients after current repair techniques [2]. The Edwards MC3 annuloplasty system and Phisio Tricuspid were recently introduced in the hope to further improve these results.

Material and Methods

Between February 2012 and April 2013, we used CEPhT ring in 64 patients at University Hospital of Salamanca, Spain. Clinical data were assessed retrospectively by thorough medical chart review. Follow-up information (eg, survival, clinical status, and most recent echocardiography) was obtained by contacting patients or referring physicians, or both, and by chart review. All patients underwent a transthoracic echocardiography. All patients had funcional TR and were classified as type I_accordidng to Carpentier's functional classification (ie, annular dilatation).

PATIENTS CHARACTERISTICS	N(%)
Female/Male	36/28
Mean age (yr)	70
Severe TR	25 (39)
Mild-Moderate TR (+ annular dilatation)	39 (61)
Moderate-Severe PAH	49 (77)
Median Euroscore I (%)	10.05
Median Euroscore II (%)	6.23

Preoperative characteristic of these 64 patients are summarized in Table 1. Patient population included 36 women and 28 men, mean age 70 years. The indications for TA were the presence of a severe TR (39%) or a slight or moderate TR associated with significant annular dilatation (61%). Moderate-severe pulmonary hypertension was present in 49 patients (77%). The expected mortality estimated with EuroScore I and II was 10.05% and 6.23% respectively.

Surgical Technique:

A small sking incision and a full sternotomy were performed in all patients. After systemic heparinization, cardiopulmonary bypass was instituted between the ascending aorta and both venae cavae. Cardioplegia using high potassium cold blood was administered in an antegrade and retrograde fashion for myocardial protection. Further myocardial protection was obtained with mild systemic cooling (33°C). We performed a right atriotomy trans-septal approach. Lef-sided valvular heart diseases were corrected first. In patients with a history of atrial fibrillation, a modified atrial Maze procedure was performed by cryothermia prior to mitral valve procedure (9%). The TA was associated with mitral valve repair or replacement (89%), aortic valve repair or replacement (39%), coronary revascularization (11%), replacement of the ascending aorta (6%), or other procedures (8%). (Tabla 2).

CONCOMITANT SURGICAL PROCEDURES	N (%)
Mitral valve repair or replacement	57 (89)
Aortic valve repair or replacement	25 (39)
Coronary revascularization	7 (11)
Atrial cryoablation	6 (9)
Replacement of the ascending aorta	4 (6)
Other procedures	5 (8)

Tricuspid valve was analyzed confirming type I dysfunction (ie, annular dilatation) in all patients. Tricuspid valve repair was performed using the CEPhT annuloplasty system. The ring is designed with a selective flexibility to help preserve natural annular movement while facilitating remodeling of the tricuspid annulus (three-dimensional wave shape). Using the Carpentier's technique of measurement, the appropriate size of the ring was selected based on the length of the attachments of the tricuspid septal leaflet and on the surface area of the anterior leaflet. Ring implantation was performed by placing a series (ie, 10 to 12) mattress sutures through the tricuspid annulus around the orifice, while avoiding the area of atrioventricular conduction tissue. The sutures were then placed through the sewing ring of the CEPhT prosthesis. Next, the ring was lowered into position and secured to the annulus. In the majority of patients, tricuspid valve repair was performed under cardioplegic arrest.

Results

In hospital mortality was 4.6% (n=3), the causes of death were right ventricular dysfunction (n=1), respiratory failure (n=1) and multiorganic system failure (n=1). Late mortality was 4.6% (n=3), the causes of death were systemic neoplasia (n=1), multiorganic system failure (n=1) and in one patient the cause of death could not be identified (Table 3).

CAUSES EARLY MORTALITY	EARLY MORTALITY N=3 (4.6%)	CAUSES LATE MORTALITY	LATE MORTALITY N=3 (4.6%)
RV dysfunction	1 (1.56)	Systemic neoplasia	1 (1.56)
Respiratory	1 (1.56)	Multiorganic system failure	1 (1.56)
Multiorganic system failure	1 (1.56)	Not identified	1 (1.56)

Survival at 16 months was 90.6%. Among the surviving patients, no cases of documented ring dehiscence, prosthetic ring endocarditis, and thromboembolic events occurred. All surviving patients showed an improvement of the New York Heart Association functional class. Ninety-seven percent of survivors (56 of 58) were in New York Heart Association functional class I or II at last follow up.

During follow-up, all patients underwent transthoracic echocardiograpahy. Table 4 shows echocardiographic results at follow-up. Left and right ventricular ejection

fraction (LVEF/RVEF) was preserved in 50 and 51 patients respectively (82 and 83.6% respectively), 30 patients (49.2%) had none to trace TR; 26 patients (42.6%) had mild TR; 3 patients had moderate TR and only 1 patient had severe TR. Figure 1 shows the echocardiogrpahic differences between pre-tricuspid annuloplasty and post-tricuspid annuloplaty.

ECHOCARDIOGRAPHIC RESULTS N (%)	LVEF	RVEF	PHT	TR
Normal	50 (82)	51 (83.6)	4 (6.5)	30 (49.2)
Mild	8 (13.1)	7 (11.5)	8 (13.1)	26 (42.6)
Moderate	2 (3.3)	2 (3.3)	31 (50.8)	3 (4.9)
Severe	1 (1.6)	1 (1.6)	18 (29.5)	2 (3.3)

Comment

This observational study reports the first series of tricuspid valve repair with the Carpentier-Edwards Physio Tricuspide ring. This prosthetic ring effectively corrects functional TR with minimal residual TR and excellent early clinical outcomes.

DIFFERENCES PHISIO TRICUSPID # MC3	EDWARDS MC3 TRICUSPID ANNULOPLASTY RING *Invented by Patrick M. McCarthy, M.D.*	CARPENTIER-EDWARDS PHYSIO TRICUSPID ANNULOPLASTY RING *Invented by Alain F. Carpentier, M.D., Ph.D.*
STRUCTURE	Rigid remodeling ring	- Selective Flexibility design - Increased Septal Segment Opening
MEASURES	Not available in 24 mm	Available in 24 mm
REFERENCE MARKERS	Anatomical reference markers on holder	Anatomical reference markers on ring
SEWING CUFF	Expansive sewing cuff	Low profile sewing cuff
CLOTH	Polyester velour cloth	Woven polyester cloth
HOLDER	Holder with lanyard system	- Angled Holder Design - Holder with surgical line of sight

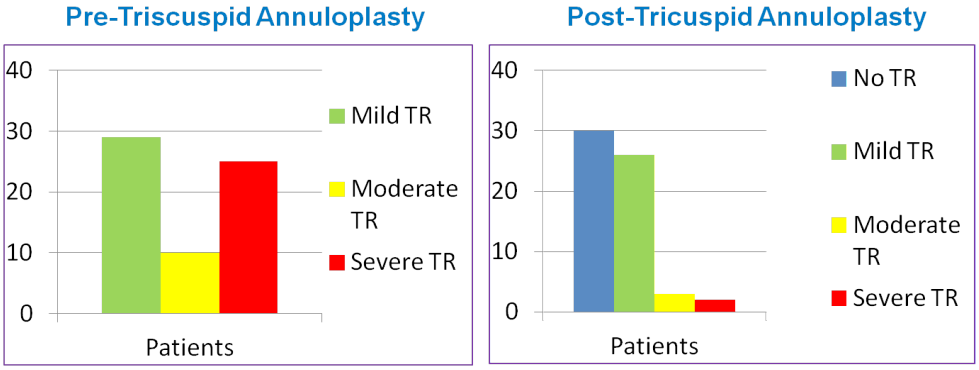
It is well accepted that significant TR (severe) should be treated at the time of surgical correction of left-sided valvular disease. However, surgical indication for the correction of mild to moderate TR remains controversial.

Untreated TR leads to poor prognosis: survival is significantly worse in patients with moderate or severe TR. If moderate or severe TR is left untreated, the survival rate for patients dropped to less than 50% in 4 years [5]

The regression of tricuspid regurgitation is unpredictable after surgical treatment of mitral and/or aortic valvular disease.

Recently, Dreyfus and colleagues suggested early surgical correction regardless of the severity of TR in patients with severe annular dilatation (>40 mm)[6]. These findings led us to adopt a more aggressive approach to tricuspid valve repair by including patients with mild to moderate TR and severe annular dilatation (diameter >40 mm).

Carpentier et colleagues suggest systematic remodeling annuloplasty regardless of the severety of TR with an annular dilatation beyond one size greater than the amount of valvular tissue. They also suggest that in TR less than mild, annuloplasty should be taken into consideration in these cases: dysfunction of LVEF, RV enlargement or PHT[1,7], which are predictors of progression of TR despite the correction of left-sided valve disease.



The concept of a remodeling tricuspid ring was developed by Carpentier more than 4 decades ago[7]. Recently, the Edwards MC3 annuloplasty system (Edeards LifeSciences) adopted this concept. It has a three-dimensional design, is rigid and pre-configured to accommodate the saddle shape of the annulus. However, in the last years a new three dimensional ring (CEPhT) has appeared to improve the MC3 ring. Table 5 shows the differences between both rings.

Our study shows that the CEPhT remodeling ring is easy to implant and reduces functional TR. Nevertheless, further follow-up and larger clinical series are required to establish the long-term stability of this repair technique.

Conclusions

The new three-dimensional tricuspid ring CEPhT is easier to implant than other previous models, corrects TR effectively and provides good short-term clinical and echocardiographic results.

After a follow-up of 16 months, echocardiogrpahic findings suggest that the tricuspid valve competence is sustained with a low rate of recurrent TR. In addition, no prosthesis-related complication (ie, prosthetic endocarditis, ring dehiscence, and thromboembolic event) occurred during this time period.

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ScienceMED, vol. 4, 1.2013, 49-54, Bologna (Italy)

Preoperative Levosimendan Treatment in High Risk Surgical Patients with Ischemic Mitral Disease

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Abstract

Objetive: Patients with chronic ischemic mitral regurgitation (IMR) have a poor prognosis, especially in those with severe left ventricular dysfunction. The present communication shows the positive effects of preoperative tratment with Levosimendan in patients with severe IMR and LVEF < 30% scheduled for CABG and mitral valve repair, even in patients without heart failure symptoms. Methods: We present two patients with severe mitral regurgitation, severe left ventricle systolic dysfunction (LVEF < 30%) and coronary artery disease scheduled for CABG and mitral valve repair, included in a study with preoperative Levosimendan therapy. Levosimendan is an inodilator agent used in short-term treatment of heart failure, improving myocardial contactility and produces systemic arterial/venous, pulmonary and coronary arteries vasodilation.We use the Levosimendan infusion during 12 hours prior to surgery (0.1 mcg/Kg/min without receiving the loading dose. Results: Case 1: 73-years-old man with three vessels disease, severe IMR, LVEF: 29.7% and severe chronic pulmonary disease (Euroscore: 11). After pre-aconditioning with Levosimendan we realized two bypasses (LIMA-AD, SV-OM(CX), non-practicable RC) and mitral valve repair, undersizing with the prosthetic ring Etlogix nº 28 and suturing the scallop between P2 and P3 using a 5/0 prolene suture. Clamp time: 98 min. CBP time: 120 min. Postoperative Echo: minimal MR with LVEF 47,3%. The patient was 10 days in ICU, and hospital discharge was 7 days after. Case 2: 80-years-old man with three vessels disease, severe IMR, LEVF: 25% and severe chronic pulmonary disease (Euroscore: 15). After pre-aconditioning with Levosimendan we realized two bypasses (LIMA-AD, SV-PD(RC), non-practicable CX) and mitral valve repair, undersizing with the prosthetic ring Etlogix nº 28. Clamp time: 112 min. CBP 120 min. Postoperative Echo: minimal MR with LEVF: 45,2%. The patient was 4 days in ICU, and hospital discharge was

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11 days after. Conclusions: Preoperative Levosimendan therapy presents an intense cardioprotective effect that improve the surgical results in patients with severe IMR and poor left ventricular function, reducing the risk of perioperative mortality.

Keywords: Ischemic mitral regurgitation, levosimendan, pre-treatment, cardiac surgery.

Introduction

Patients with chronic ischemic mitral regurgitation (IMR) have a poor prognosis, especially in those with severe left ventricular dysfunction. The present communication shows the positive effects of preoperative treatment with Levosimendan in patients with severe IMR and LVEF < 30% scheduled for CABG and mitral valve repair, even in patients without heart failure symptoms.

Although coronary artery disease and left ventricular dysfunction are related to the patient's prognosis, the presence of mitral regurgitation and its severity are independently associated with increased mortality. In ischemic mitral regurgitation (IMR) lower limits in quantitative echocardiographyc parameters have been proposed in order to evaluate the real severity of mitral valve disease (20 mm2 for effective regurgitant orifice and 30 mL for regurgitant volume).

The available data is much more limited and heterogeneous when studying IMR rather than organic mitral regurgitation. Operative mortality is higher than in organic mitral regurgitation, and long-term prognosis is less satisfactory with a higher rate of recurrence of mitral regurgitation after valve repair.

These less favourable results are due in some degree to the fact that patients with ischemic mitral regurgitation present more severe comorbidities. Most studies show that severe IMR usually does not improve by the revascularization in itself. Most patients with this valvular affection seem to benefit from valve repair with reduced size rigid prosthetic ring annuloplasty, except for those more complex and riskier cases, in which survival is similar after performing either a valve repair or a replacement [1].

Because such a few data about ischemic mitral regurgitation is available, treatment for these patients is less based on evidence. In the next table there are the indications (Tab. 1.):

	Class	Level
Surgery is indicated in patients with severe MRc undergoing CABG, and LVEF >30%.	I	C
Surgery should be considered in patients with moderate MR undergoing CABG.	IIa	C
Surgery should be considered in symptomatic patients with severe MR, LVEF <30%, option for revascularization, and evidence of viability.	IIa	C
Surgery may be considered in patients with severe MR, LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and have low comorbidity, when revascularization is not indicated.	IIb	C

Tab. 1. Indications for mitral valve surgery in chronic secondary mitral regurgitation.

In the context of congestive heart failure, previously described, we need to design new strategies to optimize the prognosis of these patients, especially in those with LVEF < 30%. Different pharmacological and physical approaches have been reported for pre-aconditioning surgical patients. In this sense, Levosimendan (LS) (Fig. 1) is a calcium sensitizer with vasodilating properties used for short-term treatment for acute heart failure. The utility of LS in the treatment for heart failure is based in a dual mechanism of action: enhancement of myocardial contractility by sensitizing troponin C to calcium and arterial and venous systemic, pulmonary and coronary by activation of smooth muscle ATP-sensitive potassium channels.

The LS increases cardiac output, coronary and renal blood flow and heart rate and decreases preload and afterload. Exerts an antiarrhythmic effect and there is evidence that it's able to reverse myocardial stunning. It's indicated for short-term treatment of patients with severe chronic heart failure acutely decompensated.

It's used intravenously and exerts its effects mainly through two mechanisms: calcium sensitization of contractile proteins in the cardiac muscle, which is associated with increased contractility, and opening of the potassium channels in the ATP-sensitive vascular tissue, causing vasodilation [2,3].

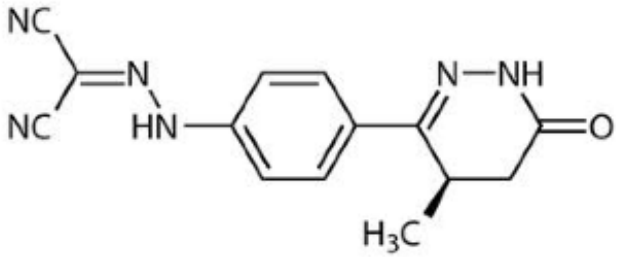

Fig. 1. Levosimendan (R){[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]hydrazono}propanedinitrile.

Although concentrations of LS decrease rapidly after stopping the infusion, the concentration of metabolites continues increasing and the peak occurs between 48 and 78 hours after stopping a 24 hours infusion. The equilibrium concentration of metabolites can be achieved within 2 weeks after starting the infusion.

Also, the benefit in the use of LS before surgery has been published in several series in cardiac surgery. The pre-treatment before surgery with LS, with enough time for not to precise a loading dose, minimizes the side effects of the drug. For example, in a study published in the British Journal of Anesthesia, LS pre-treatment versus placebo in patients who were to undergo surgery for myocardial revascularization, reduced tracheal intubation time and length of ICU stay, less inotropic support and Troponin I concentrations in the immediate postoperative period [4].

For that reasons, we propuse that preoperative coadjuvant therapy with Levosimendan could improve the surgical results in patients with coronary artery disease, ischemic mitral regurgitation and poor LEVF.

Methods

We present two patients with severe mitral regurgitation, severe left ventricle

systolic dysfunction (LVEF < 30%) and coronary artery disease scheduled for CABG and mitral valve repair, included in a study with preoperative Levosimendan therapy.

We use the Levosimendan infusion during 12 hours prior to surgery (0.1 mcg/Kg/min without receiving the loading dose. The infusion continuous during surgery and afterward, in ICU until complete 24 hour.

Actually, this protocol has been used successfully in 24 patients with different types of cardiac pathologies (coronary and not coronary artery disease, such as organic mitro-tricuspid diseases or aortic stenosis with poor LVEF).

Results

The first patients is a 73-years-old man with three vessels disease, severe IMR, LVEF: 29.7% and severe chronic pulmonary disease with an Euroscore: 11.

After pre-aconditioning with LS we performed two bypasses (LIMA-AD, SV-OM (CX), nonpracticable RC) and mitral valve repair, undersizing with the prosthetic ring Etlogix nº 28 and suturing the scallop between P2 and P3 using a 5/0 prolene suture. Clamp time: 98 min. CBP time: 120 min. Postoperative Echo: minimal MR (Fig. 2) with LVEF 47,3% (Fig. 2). The patient was 10 days in ICU, and hospital discharge was 7 days later.

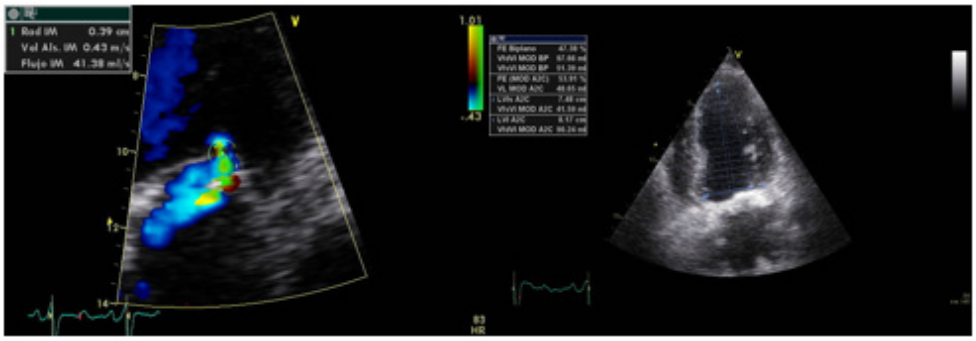

Fig. 2. These figures shows minimal mitral regurgitation and the increased left ventricular ejection fraction after surgery.

The second patients is a 80-years-old man with three vessels disease, severe IMR (Fig. 3), LEVF: 25% (Fig. 3) and severe chronic pulmonary disease with an Euroscore: 15.

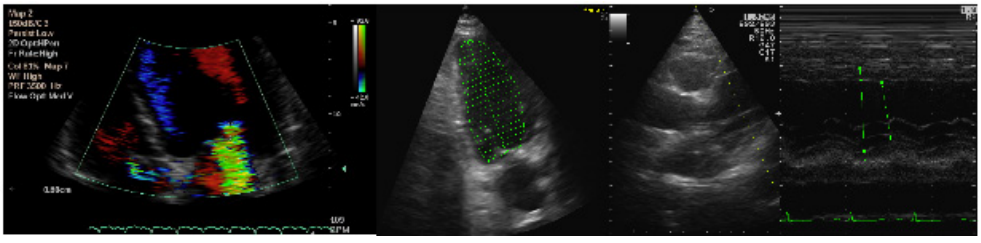

Fig. 3. These figures shows severe ingurgitation mitral and poor left ventricular ejection fraction.

After pre-aconditioning with LS we performed two bypasses (LIMA-AD, SVPD (RC), non-practicable CX) and mitral valve repair, undersizing with the prosthetic ring Etlogix nº 28. Clamp time: 112 min. CBP 120 min. Postoperative Echo: minimal MR (Fig. 4) with LEVF: 45,2% (Fig. 4). The patient was 4 days in ICU, and hospital discharge was 11 days later.

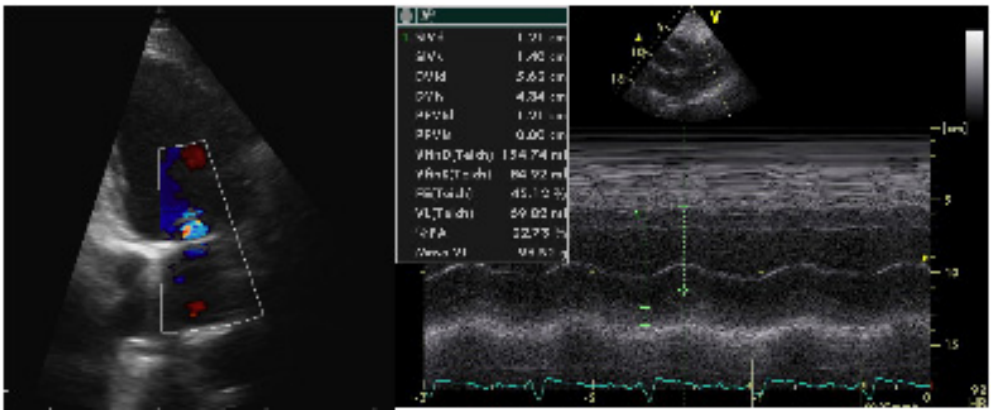

Fig. 4. These two figures shows the result after cardiac surgery: minimal mitral regurgitation and increased of left ventricular ejection fraction.

Discussion

Cardiac surgery can produce varying degrees of myocardial stunning afterwards, which causes varying degrees of transitory myocardial dysfunction. Over the years different approaches have been tried for myocardial protection through preconditioning with short periods of ischemia, and anesthesic agents [5]. In the same line, recently published studies have shown some cardioprotective effect of LS on patients undergoing cardiac surgery when using it before the intervention, demonstrating positive effects on the reduction of the time of ICU stay and mechanical ventilation, troponin levels and postoperative need for inotropic drugs in the immediate postoperative period [6].

The pre-treatment with LS will protect the heart against ischemia–reperfusion damage. There are studies that shows that LS open KATP channels in the cell plasma membrane also have been shown to act on KATP channels in mitochondria. There is a consensus that the opening of mitochondrial ATPsensitive potassium (mitoKATP) channels protects the heart against ischemia–reperfusion damage [7, 8]. The increased potassium influx associated with mitoKATP channel opening is sufficient to preserve mitochondrial function in situations of distress such as ischemia and/or reperfusion. The connection between the opening of mitoKATP channels and the phenomenon of cardiac preconditioning has created potential new uses for potassium channel– opening drugs in myocardial ischemia and in this case in pre- and perioperative context [9, 10].

Also LS improves ventricular-arterial coupling and the cardiovascular "performance" of coronary patients with severe left ventricular dysfunction, through two mechanisms, reducing arterial elastance and reducing myocardial contractility [11].

Patients with chronic mitral valve disease are at particular risk for severe right ventricular failure after cardiopulmonary bypass, because of low cardiac output and

pulmonary hypertension. The ability of LS to increase contractility and decrease pulmonary vascular resistance, combined with its minimal metabolic cost and low potential for arrhythmias, affirms its status as a potentially useful addition for the treatment of such patients [2, 12].

The preoperative use of Levosimendan would be justificated because of the cardio-protective effect against ischemia-reperfusion injury and the preparation for the occurrence of severe hemodynamic changes during intraoperative and postoperative steps, in patients with a severely depressed ventricular function [2, 13, 14].

In conclusion, our results suggests that preoperative Levosimendan therapy presents an intense cardioprotective effect that improve the surgical results in patients with severe ischemic mitral regurgitation and poor left ventricular function, reducing the risk of perioperative mortality. However, prospective studies are necessary to verify the utility of this drug as a coadjuvant therapy in cardiac surgery procedures.

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ScienceMED, vol. 4, 1.2013, 55-59, Bologna (Italy)

Influence of Target Vessel, Conduit type and Graft Configuration in Mean Intraoperative Blood Flow of Aorto-Coronary Bypass Grafts

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Abstract

Intraoperative aorto-coronary graft flow magnitude reflects the quality of myocardial revascularization. It is associated with graft patency and clinical outcome. However, there is little information relative to normal flow values concerning to target vessel, conduit type and graft configuration.

We recorded the mean flow (MF) in ml/min of 1891 aorto-coronary grafts performed in 729 patients. Conduits used consisted of: major saphenous vein (SV) in 1034 cases, left internal mammary artery (LIMA) in 634, right internal mammary artery (RIMA) in 140 and radial artery (RA) in 83. There were 1583 simple and 308 sequential grafts. Flow was measured at the end of the intervention using a transit-time method based flowmeter (Butterfly, MediStim).

The average MF was 34.8±9 ml/min. MF was significantly higher for sequential than for simple bypass grafts, both in the global analysis (44.4 vs. 32.9, $p < 0.0001$) as in each target vessel. The MF of simple grafts was higher in RIMA grafts (36 ml/min) and in those destined to obtuse marginal (OM) branches and right coronary artery (31 ml/min). MF of sequential grafts was also higher in those anastomosed to OM branches (47 ml/min) and in those performed with SV (44 ml/min).

Intraoperative graft flow depends on the target vessel, the type of conduit and its configuration. In simple bypass grafts, higher MF was found in squeletonized RIMA grafts anastomosed to the OM. Concerning sequential grafts, a significantly higher MF was detected in those constructed with SV and destined to the OM.

Keywords: Coronary surgery, aorto-coronary-grafts, flow measurement

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Introduction

Intraoperative flow measuring in aorto-coronary bypass grafts is a very useful tool for quality assessment in coronary surgery. Mean flow (MF) has been related to graft patency and long-term clinical outcomes. However, few information exists relative to normal flow values, the relationship between type and configuration of the conduits, and the characteristics of the target vessel.

Patients and methods

The MF (ml/min) was recorded at the end of the intervention in 1891 grafts performed in 729 patients. We used flowmeters based on the transit time method (Butterfly and VeriQ, MediStim, Oslo, Norway) and perivascular probes of different sizes. Records of poor quality or possible dysfunctional grafts were not included in the analysis. The conduits used were the great saphenous vein (SV) in 1,034 cases, left internal mammary artery (LIMA) in 634, the right internal mammary artery (RIMA) in 140 and the radial artery (RA) in 83 cases respectively. Related to the type of coronary anastomosis, a total of 1583 simple and 308 sequential grafts were registered.

The relationship of the MF with the type and configuration (simple or sequential) of the conduit, and the type and character (principal or secondary) of the target vessel, was analyzed using non-parametric test (Wilcoxon/Kruskall-Wallis) and logistic regression. Data are presented graphically as box plots with the median, interquartile range and 90% confidence limits. Vessel character was nor analyzed in sequential grafts because the frequently different characteristics of the involved coronary arteries.

Results

The median of the mean flow for overall cases included was 31(21-44) ml/min. The MF was significantly higher for sequential than for simple grafts (42 vs 29 ml/min, $p < 0.0001$) (Fig. 1).

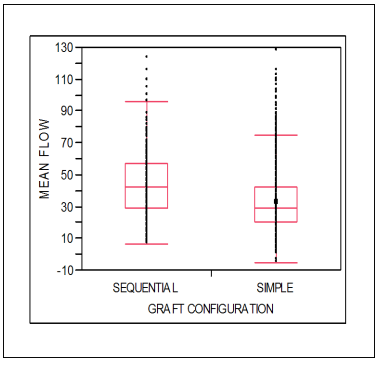

Figure 1. Median value of the mean flow (ml/min) recorded in simple and sequential grafts.

MF was also higher in sequential than in simple grafts for each main coronary territory. Sequential grafts had a MF between 20 and 40% higher than simple grafts destined to the same territory. The greater increment was found in the circumflex

artery territory (47 vs 31 ml/min, $p < 0.001$), followed by the LAD territory (37 vs 27 ml/min, $p < 0.01$) and the RCA territory (36 vs 30 ml/min, $p < 0.05$).

In simple grafts, we found no relationship in terms of the MF in those grafts destined to principal or secondary vessels (Fig. 2-A). Also, we found the highest MF in grafts destined to circumflex marginal branches and to the main right coronary artery, both with 31 ml/min (Fig. 2-B), as well as in RIMA grafts, 37 ml/min (Fig. 2-C).

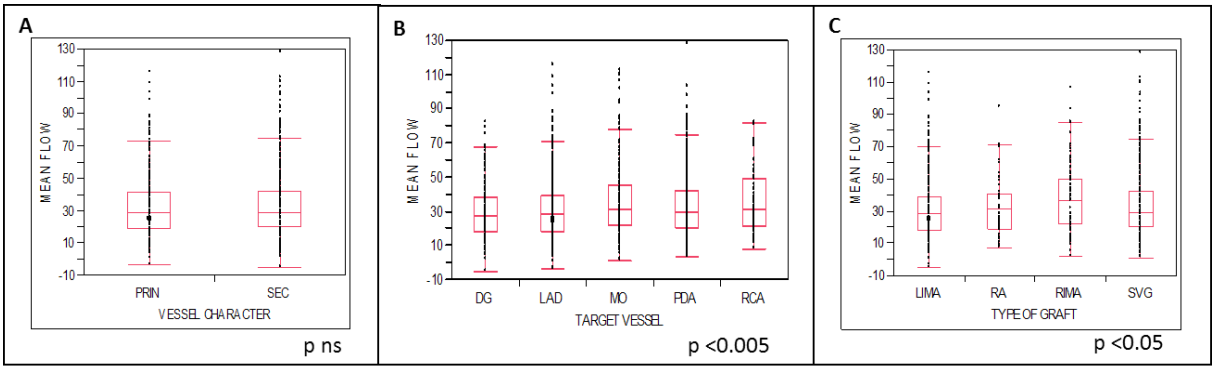

Figure 2: Median value of the mean flow in simple grafts according to the vessel character (A), target vessel (B) and type of conduit (C).

Regarding sequential grafts, MF was also higher in those anastomosed to circumflex marginal branches, 47 ml/min (Fig 3-B), and in those made of SV, 44 ml/min, and RIMA, 42 ml/min (Fig 3-C).

In multivariate analysis, only graft configuration (simple or sequential) emerged as an independent graft MF predictor.

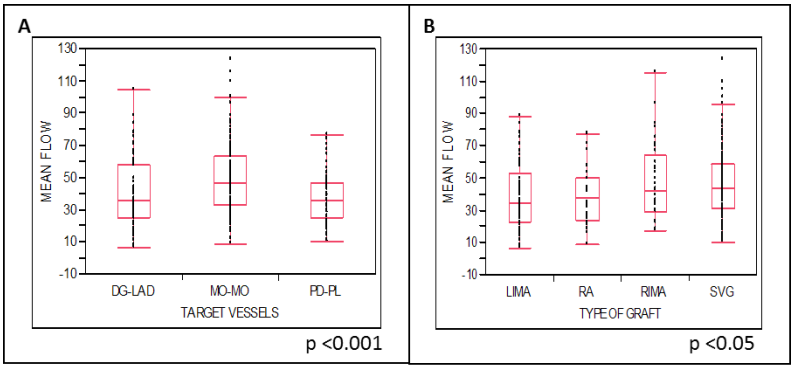

Figure 3 Median value of the mean flow in recorded for sequential grafts according to the target vessel (A) and type of conduit (B).

Discussion

Flow measurement of aorto-coronary grafts at the end of the intervention reflects the quality of the revascularization achieved with surgery. Somehow, this measure

reflects the benefit provide by surgery in myocardial perfusion. Thus, flow measurement in coronary surgery had become a quality of care tool, both in off-pump and in standard on-pump coronary surgery.

The MF of grafts reflects the amount of blood provided by the graft to the myocardium and it is the most widely used measuring parameter (CITA 1). Among the different technologies available to assess the flow of grafts, transit time-based devices have become the most commonly used because of their reliability and high performance (CITA 2). Transit time-based devices also allow to quantify some additional parameters as maximum and minimum flow provided by aorto-coronary grafts, as well as the proportion of flow supplied during systole and diastole. In addition, they can quantify, among others, different parameters of coronary flow, such as the pulsatility index, the percentage of reverse flow, and the derivate of flow with respect to the time. All of them asses the quality of blood flow provided by aorto-coronary bypass grafts.

The finding of a higher MF in sequential grafts is not surprising; the perfusion of more than one vessel increases the graft run-off, providing greater MF. This fact is a well-known advantage of sequential grafts (CITA 3). This benefit should be added to the ability to reduce the number of grafts and proximal anastomosis needed when this type of conduit is used. However, the MF achieved with a sequential graft destined to two different vessels of a particular territory is usually lower than can be achieved using two different grafts. Surgeons should carefully assess the potential advantage of a greater initial flow versus the possibility of a better long-term patency in each particular patient.

More surprising is the lack of influence of the character of the target vessel, primary or secondary, in the MF. It could be expected that principal vessels, perfusing a more extensive myocardial territory, would have greater MF. The lack of influence of the character of the target artery probably reflects a poor definition of this variable; is possible that some secondary vessels perfuse a significant amount of myocardium and that the influence of additional parameters, such as the severity of proximal stenosis and distal bed quality have not been taken into account.

It is also surprising the finding of a greater flow in coronary branches dependent of the circumflex artery, especially in the sequential grafts. One might have expect that the largest MF had corresponded to the vessels of the anterior face of the heart, especially the LAD. The determinants of this finding may be the same people who have been mentioned in the previous section.

In our experience, the greater MF was recorded in grafts of RIMA, both in the simple configuration as in sequential one. On the other hand, the lower MF corresponded to LIMA grafts. RA and SV grafts provided intermediate flows, although the SV presented more MF in sequential grafting. The cause of the greater flow capacity of the RIMA is probably related to the harvest technique; while the LIMA was harvested with all its pedicle, the RIMA was harvested in squeletonized way to preserve the sternal perfusion in patients in which both mammary arteries were used. The skeletonization of the AMI implies a sympathetic denervation which has been shown to improve the flow of this conduit type (CITA 4).

When assessing our findings, it is necessary to consider some important limitations. It is well known that the flow in the aorto-coronary grafts is closely related with the severity of the proximal stenosis of the target artery and vessel run-off (CITA 5). This

fact is mainly determined by the development of the target vessel, the presence of diffuse disease in the distal coronary bed and the viability of affected myocardium. None of these variables had been taken into account in our study.

On the other hand, hemodynamic conditions at the time of flow measurement have a relevant influence in the graft flow estimation. Although all our measurements were performed once the patient was weaned from cardiopulmonary bypass and in stable hemodynamic conditions, it is possible that variations in blood pressure or cardiac output may have influenced our results.

Conclusions

In addition to other factors not analyzed in this study, intraoperative flow in aorto-coronary bypass grafts depends on the characteristics of the target vessel, and the type and configuration of conduit. We found that MF was higher in grafts destined to branches of the circumflex artery and those made of RIMA and SV. However, only the sequential configuration of conduits was independently associated to a higher flow. We consider that these values can serve as reference for evaluating the quality of surgical revascularization.

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ScienceMED, vol. 4, 1.2013, 61-68, Bologna (Italy)

Improvement of transcranial ultrasound uniformity by random modulation

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Abstract

It is known that transcranial ultrasound irradiation can enhance the effect of thrombolytic agent tissue plasminogen activator (tPA) depending on the intensity. Because of the interference properties of ultrasounds, the ultrasound beam is inhomogeneous in the near-field region of the transducer i.e. there are low-intensity (cold) spots of the ultrasound and high-intensity (hot) spots. The inhomogeneous distribution can be problematic for sonothrombolysis, because the effect of the tPA cannot be enhanced at the cold spots and the risk of haemorrhage is higher at the hot spots. In this work, we showed that the cold and hot spots problem can be resolved by *random modulation* of the activating signal, which was first introduced in order to reduce the standing waves in the skull. In particular, we investigated the random modulation method which inverts the phase of the sinusoidal wave at random timing. We compared the random modulation method with sinusoidal one. In order to quantify the uniformity of the ultrasound field, we used *Uniformity Index (UI)*, which was defined by authors. By the definition, it is inferred that the smaller value of UI means the more homogeneous field. We calculated the UI from the field distribution obtained by hydrophone measurement. While the UI was 306 for sinusoidal wave in the free-field (without any obstacle) case, it was 213 for randomly modulated wave. In the case of passing through the temporal bone fragment, the UI was 566 for sinusoidal wave and 266 for randomly modulated wave. It was shown that random modulation method can resolve cold and hotspots problem as well as standing wave problem. The present study is expected to be useful for the development of safer and effective transcranial therapeutic equipment.

Keywords: *Sonothrombolysis, random modulation, uniformity*.

Introduction

Recently it has been clinically shown that transcranial ultrasound irradiation helps

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the dissolution of thrombus and increases the recanalization rate by enhancing the effect of the tissue plasminogen activator (tPA) [1]. The enhancement depends on the intensity of the ultrasound. If the intensity is too low, the effectiveness is lost. However, if the intensity is too high, the risk of cell damages can be higher and cerebral haemorrhages might be caused. Hence, it is important to keep the intensity in the suitable range.

Because of the interference properties of the ultrasound, the intensity distribution of the ultrasound is inhomogeneous near the transducer; there are many lower-intensity cold spots and higher-intensity hot spots (see Fig. 1 below). In order to realize the effective and safer sonothrombolysis, it is desirable that the cold and hot spots are reduced. We hypothesized that the certain modulation of the activating signal to the transducer for the ultrasound emission reduces the cold and hot spots. In particular, *random* modulation was investigated in this study.

Random modulations have been studied for the purpose of the standing wave reduction in the skull [2-4]. The standing wave is considered to be the cause of the cerebral haemorrhages [5], which occurred in TRUMBI trial [6]. In ref [7], it was experimentally shown that the random modulation can reduce the standing wave. One of the most effective methods was Random switching of both inverse carriers (RSBIC). In RSBIC signal, the phase of the sinusoidal wave is inverted at random timing.

The purpose of the present study is to experimentally verify that RSBIC method can reduce the cold and hot spots or improve the uniformity of the ultrasound intensity distribution.

Method

1.1. Random modulation method

RSBIC activation method is one of the random modulation methods and one of the most successful methods for standing wave reduction [4]. We investigated the effect of the RSBIC signal on the inhomogeneous distribution of ultrasound intensity. (An intensity distribution near the transducer is shown in Fig. 1). Here, we reproduce the description of RSBIC signal.

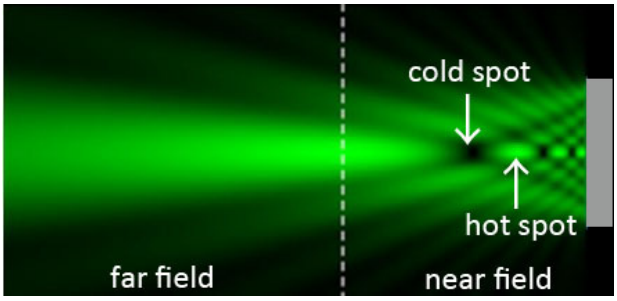

Fig. 1 An inhomogeneous distribution of the ultrasound intensity near the transducer is shown (numerical result). The diameter of the transducer is 24mm and the frequency is 500 kHz. The medium is water. The density of the water set to be 1.0g/cm^3 and the sound speed to be 1500m/s.

The RSBIC signal S as a function of time t is described by $S(t)=A \sin [2\pi f_0 t+\varphi(t)]$,

where A is the amplitude, f_0 is the carrier frequency, 500 kHz in this study, and φ(t) is the phase angle which depends on t. The value of φ(t) is controlled to be either 0 or π. Whereas for the case in which φ=0, the signal S(t) belongs to the *normal carrier*, for the case in which φ=π, the signal belongs to the *inverse carrier*. The RSBIC signal is realized by switching between these two carriers at each time of random interval. An example of the waveform of the RSBIC signal is shown in Fig. 2. The ordinary sinusoidal wave is also shown in Fig. 2.

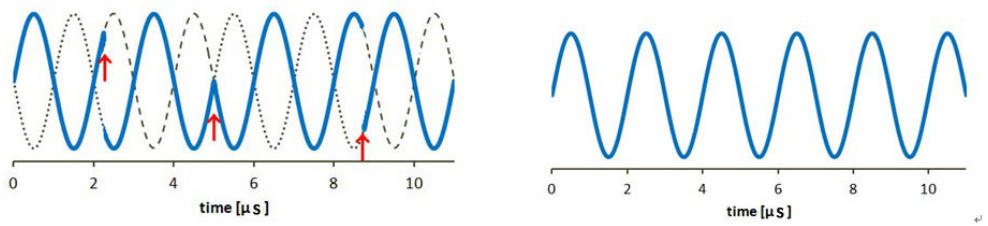

Fig. 2 (left) An example of RSBIC waveform. The inversions of the phase are indicated by the red arrows. The dotted line indicates the normal carrier and the broken line indicates the inverse carriers. The frequencies of both normal and inverse carriers are 500 kHz and the periods are 2μs. The RSBIC signal is made by the switching of between the two carriers at each time of random intervals. (right) A waveform of sinusoidal signal. The frequency is 500kHz, and the period is 2μs.

In order to generate the RSBIC signal, we constructed a special custom-made circuit in our experiment. The timing of switching between normal carriers and inverse ones is electrically determined by the zero-cross timing of the thermal noise. The source of the noise exists in the circuit and we used the noise filtered by low pass filter and high-pass filter. The lower and upper cut-off frequencies of the noise are the parameters of RSBIC activation method. We set the lower cut-off frequency to be 50 kHz (10cycles) and the upper cut-off frequency to be 200 kHz (2.5cycles) as representative values.

1.2. The measurement of the ultrasound intensity

The transducer we used has 511 kHz as center frequency and 308 kHz of bandwidth. This wide bandwidth is suitable for the random modulation because many waves of different wavelength can be superimposed. The diameter of the transducer is 24mm. The wavelength of the ultrasound wave is about 3mm in water at the frequency of 500 kHz.

Fig. 3 shows a diagram of the experimental setup for the measurement of the intensity distribution. The sinusoidal wave was generated by the signal generator (AFG3102; Tektronix, OR, USA). Then, the sinusoidal wave was converted to RSBIC signal S(t) by the special custom-made circuit, which was not needed for sinusoidal case. After the signal was amplified by Amplifier (HSA4101; NF Corporation, Japan), the signal was applied to the transducer.

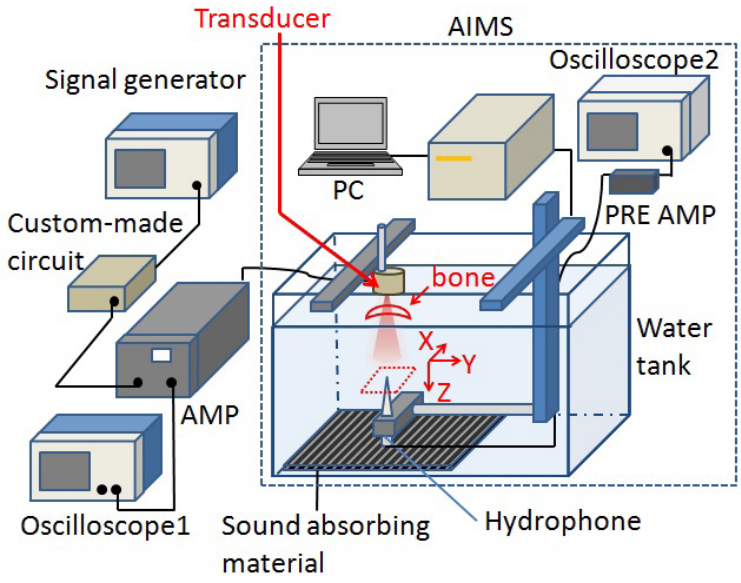

Fig. 3. An experimental setup for scanning of the ultrasound intensity.

The measurement of the intensity distribution of ultrasound was performed by an acoustic intensity measurement system AIMS (Onda corporation, CA, USA) with a hydrophone having an active tip of 0.4 mm in diameter and a wide bandwidth of frequency (from 100 kHz to 10 MHz). We calibrated the hydrophone at 500 kHz. The precise position of the hydrophone can be controlled by PC and the measurement of the intensity distribution was automated. A fragment of temporal bone was put in between the transducer and the hydrophone. Monitoring the received signal by an oscilloscope2 (DSO6012A: Agilent Technologies, MA, USA), we measured the temporal average of the ultrasound intensity for 500μs on the two-dimensional plane parallel to the transducer surface. The data were acquired in the range of 40mm ×40mm with a step of 1mm for both directions. The distance from the transducer was 15mm, at which cold spot can be clearly seen in the sinusoidal case.

1.3. Definition of the uniformity index

In order to quantify the uniformity of the ultrasound intensity distribution, we use uniformity index, which was firstly introduced and defined in ref [15]. Here, we reproduce the mathematical definition of two-dimensional uniformity index UI_{2D}.

Let f(x, y) be the acoustic intensity (or pressure amplitude) of the ultrasound field on the two-dimensional (x, y) plane. The two-dimensional uniformity index UI_{2D} is defined by the following formula (1).

$$\mathrm{UI_{2D}} = \frac{\int\sqrt{\left(\frac{\partial f}{\partial x}\right)^2 + \left(\frac{\partial f}{\partial y}\right)^2}\,dxdy}{\int f(x,y)dxdy} \quad \ldots\ldots(1)$$

It has the dimension of [Length^{-1}]. If the ultrasound intensity has many steep

peaks and troughs, the value of f(x, y) will be varied considerably depending on the position. Since the contribution of the derivative terms is larger in that case, the index becomes large. In an opposite manner, the ultrasound is considered to be more homogeneous if the index decreases.

The expression (1) has the following properties: (i) intensity independence and (ii) rotational invariance. The intensity independence means that the index is invariant under the transformation f(x, y)→αf(x, y), where αis constant value. Hence, the index can be determined irrespective of the applying voltage of the transducer. The rotational invariance means that the index is unchanged under the transformation

$$\begin{cases} \xi = \cos\theta x + \sin\theta y \\ \eta = -\sin\theta x + \cos\theta y \end{cases} \quad \ldots\ldots(2)$$

where θ is the angle of rotation. Therefore, the index is independent of the direction of x-coordinate.

Result

In Fig. 4, we show the two-dimensional distribution of ultrasound intensity in the case of free-propagation in water without bone. The left figure was obtained by sinusoidal signal, whereas, the right one by RSBIC signal. The cold spot can be clearly seen at the center in the sinusoidal case. However, in the case of RSBIC, the distribution is more homogeneous and the cold spot disappears. The UI_{2D} is 306 for sinusoidal case and 213 for RSBIC case. The UI_{2D} is smaller for RSBIC, as expected.

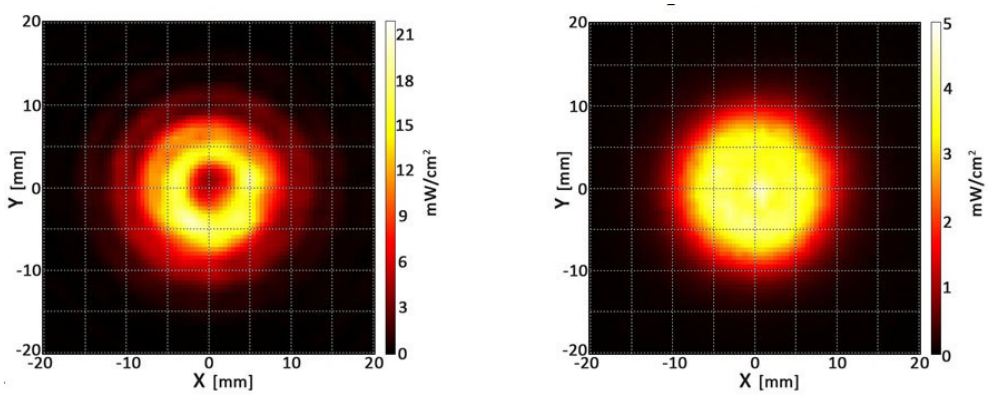

Fig. 4 Two-dimensional distribution of ultrasound intensity without bone for sinusoidal signal (left) and RSBIC signal (right). The UI_{2D} is 306 for sinusoidal case and 213 for sinusoidal case. The carrier frequency was 500k Hz and the activating voltage was 13.3 Vpp. The band of the noise which was used for RSBIC signal was from 50 kHz to 200 kHz. The diameter of the transducer was 24mm. The distance from the surface of the transducer was 15mm.

Fig. 5 shows the intensity distribution in which the ultrasound passed through the fragment of temporal bone. Since the ultrasound was distorted by the transmission of the bone, the intensity distribution is more inhomogeneous than without bone. It

can be seen that randomly modulated wave improve the uniformity of the intensity distribution. In particular, the cold spot at the (X=2, Y=1) disappeared in the RSBIC case. The UI_{2D} is 566 for sinusoidal case and 266 for RSBIC case.

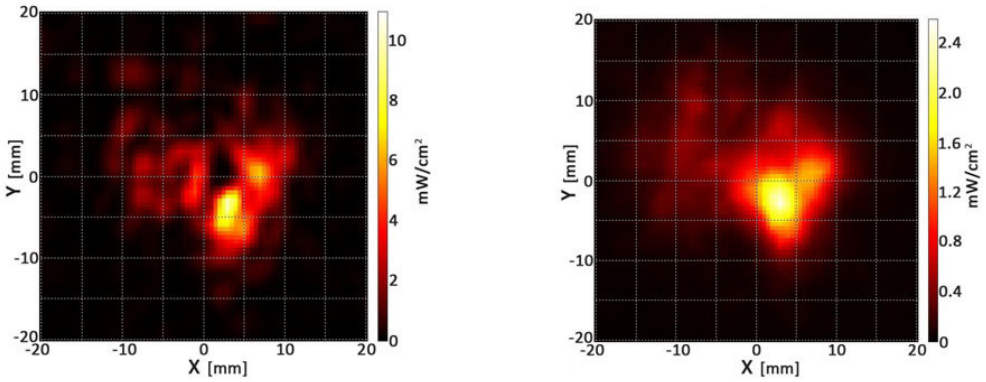

Fig. 5 Two-dimensional distribution of ultrasound intensity with bone for sinusoidal signal (left) and RSBIC signal (right). The UI_{2D} is 566 for sinusoidal case and 266 for sinusoidal case. The carrier frequency was 500k Hz and the activating voltage was 13.3 Vpp. The band of the noise which was used for RSBIC signal was from 50 kHz to 200 kHz. The diameter of the transducer was 24mm. The distance from the surface of the transducer was 15mm

Conclusion

It was shown that RSBIC method can reduce the cold and hot spots or improve the uniformity of the ultrasound intensity distribution in the case of through/without bone. The improvement of the uniformity was quantitatively verified by the calculation of the uniformity index. Since the RSBIC method can resolve both of the standing wave problem and cold-hot spots problem at the same time, it is attractive for therapeutic usage of ultrasound. A therapeutic equipment based on the sonothrombolysis with de-focused ultrasound is being developed in collaboration with the animal experiment [8].

Acknowledgment

The present study was supported by a Grand for Research on Advanced Technology (H21-008) from the Ministry of Health, Labour, and Welfare of Japan.

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ScienceMED, vol. 4, 1.2013, 69-71, Bologna (Italy)

The Advantages of Using CBCT in Maxillofacial Imaging

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Summary

In this article we evaluate the main advantages and disadvantages of the CBCT (cone beam computed tomography) in maxillofacial imaging. The study was conducted on over 1000 patients that were investigated through x-ray, panoramic radiographs and CBCT over 5 years. The main pathology was represented by cysts, traumatisms, benign and malign tumors. We also evaluated the dental implants through CBCT. The conclusion was that CBCT is cost effective; the radiation dose was almost similar to that of a panoramic view. In dental implants treatment it provides very useful measurement details (both 2D and 3D).

Introduction

During the last years the imaging modalities used in investigating the maxillofacial region such as digital imaging, computed tomography, magnetic resonance imaging, positron emission tomography and cone beam computed tomography) are developing very fast. They provide high quality new images that continually contribute to the improvement of the diagnostic tasks.

Materials and Method

The study was conducted on over 1000 patients from VIVAS DENT clinic from Arad, Romania, over a period of 5 years. The patients were investigated through retro-alveolar radiographs, panoramic radiograph and cone beam computer tomography (CBCT - using a KODAK 9000 3D System).

After the clinical investigation we performed a panoramic view. If it was suspected

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a cyst, tumor (benign, malign) or a traumatism we performed a CBCT. Also, to all the patients who were subjects to implants was performed CBCT. Retro-alveolar radiographs were initially used if we suspected caries, periapical inflammation.

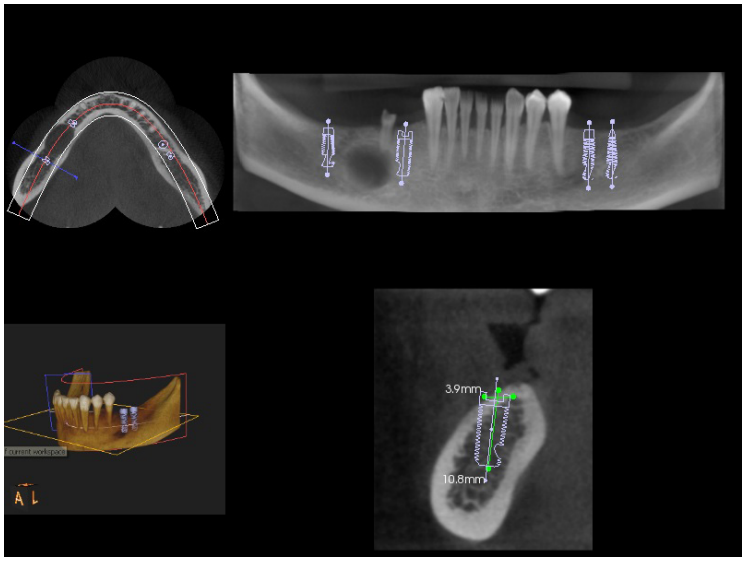

Figure 1. CBCT scan of a patient with a radicular cyst on the body of the mandible (anterior, superior and lateral view), 3D reconstruction, showing the future location for the implants.

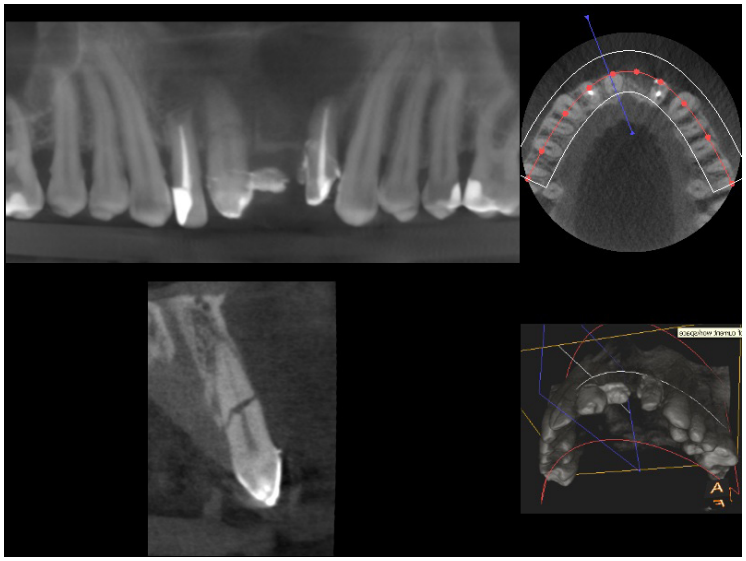

Figure 2. CBCT of a patient with radicular fracture – left superior incisive (anterior, superior and lateral view), 3D reconstruction

Results

Using these imagistic techniques we detected 76 new cyst, 1 malign tumor.

The main benefit of CBCT was for the implant team. The software we used can link the implant, abutment and virtual restoration, generating and interactive treatment planning.

Conclusions

CBCT should be used only after a through clinical examination, and if it expected to provide a better diagnostic. This imaging technique provides 3D volumetric data reconstruction of the maxillofacial structures.

The dose of radiation in a CBCT scan (with our equipment) was similar to that of a panoramic exam. Also the radiation dose may vary with different machines.

CBCT is best used in implant dentistry to determine the bone height, density and for nerve tracking.

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ScienceMED, vol. 4, 1.2013, 73-78, Bologna (Italy)

Biological and molecular characteristics, diagnosis and treatment of triple negative breast cancer

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Abstract

Carcinoma of the mammary gland is an issue of social importance. Frequency is constantly rising, imposing in-depth study. By applying immune-histochemical and genetic research, it has helped introduce several molecular subtypes of breast cancer. One is triple negative cancer / TNC / with ER, PR, HER2 negative status. It features an extremely heterogeneity in terms of their molecular and genetic characteristic.TNC occurs with more aggressive than other breast cancer subtypes and manifests with early recurrence, frequent visceral metastases, shorter overall survival. These features have led to its detailed study. In this context, TNCs are divided into several subtypes with specific immune-histochemical and genetic characteristics. Discovering of new molecular markers, gives light in the study of TNCs. This is related to the prognosis of the disease, the way and the type of therapy. Discoveries at genetic and molecular level of TNCs are related to the introduction of new target therapy, which will lead to better results in *the treatment of this aggressive type of breast gland. All this is a step forward in the implementation of individualized therapy for TNC.*

Key words: *triple-negativnen cancer, molecular subtypes, molecular markers, genetic testing, immunohistochemical examination, treatment, therapy target*

Introduction

The incidence of breast cancer in the last 25 years has increased by 30%. 1.4 million new cases have been registered annually. In Bulgaria frequency of breast cancer is 22.8%. Triple negative cancer, characterized by ER, PR and HER2 negative status is about 15-20% of newly diagnosed cases of breast cancer.

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Etiological factors associated with its development are varied. Careful study of the biological characteristics of triple-negative tumors is extremely importantl. That is imposed by the fact that this tumor is extremely heterogeneous. It is linked to its genetic predisposition. Thorough genetic analysis sheds new light on understanding the biology of triple-negative cancer. Analysis of the gene profile may provide an information about prognosis and sensitivity to the treatment. Its conduct is not always possible. That requires in routine practice to use immunohistochemical analysis of molecular markers thef treatment to be specified , and prognosis of the illness. In the recent stage triple negative cancer itself is divided into several subtypes based on immunohistochemical typing reasoned by the unique genetic characteristics: basal – cell (BL1, BL2), immunomodulating IM, mesenchymal M, mesenchymal – stem MSL, luminal-type androgen receptor LAR. Each of these subtypes is characterized by the expression of certain biomarkers, activation of various signaling pathways, which is the basis of the specific target terapy. Recently the best studied are following biomarkers-cytokeratin 5/6, 14,17, EGFR, vimentin, cadherin , Ki67, p53, caveolin1, 2, cristaline and dr. The damage of BRCA1 gene involved in DNA replication is also associated with a triple negative cancer There are data that 90% of the mutated BRCA1 tumors are triple negative, or a basal epithelial phenotype.

Genetic and related with it molecular characterization of triple negative cancer are followed by the peculiarities of its course. It features with more aggressive course of development, expressed in early metastasis, frequent local recurrence, more frequent visceral metastases, actually with more poor prognosis. Standard chemotherapy regimens are mainly used in patients with TNMBC. It is proven the advantage of anthracycline and a taxane-containing regimens for adjuvant and neoadjuvant chemotherapy. Adjuvant docetaxel-based chemotherapy improves disease-free interval (DFS) and overall survival (OS). It was found an advantage in relation to Cisplatina in neoadjuvant treatment in terms of pathological response (p CR).

Treatment of metastatic triple-negative cancer is extremely difficultl task. Conventional therapies for patients with recurrences and metastases are limited, because the standard chemotherapeutic regimens containing anthracyclines and taxanes are now administered as adjuvant and neoadjuvant chemotherapy. Other reason for treatment failure is multidrug resistance. The main drugs administered in monotherapy or in combinations are: Docetaxel, Paclitaxel, Capecitabin, Ixabepilon, PARP-inhibitors, Eribulin, VFGF inhibitors, tyrosine - kinase inhibitors, blockers PI3K/mTOR, and new target treatment.

Modern oncology requirements are associated with an individual approach to each potsient, which requires accurate diagnosis, proper treatment selection and algorithm of follow up. Unresolved problems in diagnosis and treatment of TNMBC us determine our study. The aim of this study was to examine in detail some of characteristics of women with TNBC in Bulgarian population through examination of panel molecular markers and gene mutations in order to determine optimal treatment tactics and improve prognosis.

Materials and Methos

1. In the present study have been included 100 women with metastatic triple negative breast cancer. They have gone on treatment in the Department of Medical Oncology at the Centre of Sofia for the period from 2005 to 2012. They had histologically

proven breast cancer and immunohistochemical ER, PR, HER2 receptor-negative status. For comparison, were followed up 30 women of the same index, who were with non- metastatic triple negative cancer. The patients were monitored for the following parameters: frequency age, morphological characteristics of the tumor, tumor volume, histologic type, stage of disease, the number of samples and the number of metastatic lymph nodes, grade, of malignancy, follow up of DFS based on adjuvant chemotherapy-division 100 patients into 3 groups, 1 g. Held adjuvant anthracycline chemotherapy, 2 g. Adjuvant anthracycline / 4 rate FEC / +4 course Docetaxel, 3 g. naïve no adjuvant therapy; follow up of PFS patients separated in three groups by type of first-line chemotherapy for metastatic disease, 1 g. Initial treatment with Paclitaxel qw + Bevasizumab 10 mg / kg 1-15 days, 2 g. conducted first-line chemotherapy with taxanes, 3 groups chemotherapy with other agents-Capecitabin, Navelbin and others. To elucidate the biological characteristics of metastatic triple negative cancer were examined 63 patients and monitored the frequency of a panel of molecular markers 7-Cytoceratin 5/6, Ki67, Cytocertin14, VGFR, EGFR, Caveolin1, AR.

Resuts

The observed average age incidence in patients was 51.16 (+/–10.393) years. The minimum age is 25 and the maximum age is 74 years. The average age incidence was not statistically different in the groups (p = 0,061). Patients were divided into following age categories: under 40, 11, 2% 40-65 years 80.8%, 65 years 8.0%.

Examined by histological type metastatic triple negative cancer, we found that the predominant invasive ductal cancer followed lobular and other types: 1 - group followed up patients with adjuvant anthracyclines 70% e invasive ductal carcinoma, invasive lobular 20,7%, 5, 2% ducto-lobular, 3.4% other types, 2 - group with adjuvant anthracycline and taxane-36.8% invasive ductal, invasive lobular 21.1%, 31.6% ducto-lobular, 10, 5% of other, for the third group did not carry out adjuvant - 50.0% is invasive ductal carcinoma, 5.0%, is an invasive lobular carcinoma, 15,0% is works-lobular, 30.0% is the other, for the control group with non-metastatic disease: 74.2% invasive ductal carcinoma, 3.2% invasive lobular carcinoma, 9.7% ducto-lobular carcinoma, 12.9% others. Statistically significant association was found between histological types and groups of patients (p = 0.003). Patients held adjuvant chemotherapy prevalent invasive ductal-type, while those who did not receive adjuvant therapy different types predominate.

According to the size of the tumor was found that 2.11 cm (+/–1.039) is the average size of tumor diagnostics. (P> 0,05). Patients were divided into two groups: with size less than 2 cm -26 patients (25.7%)] with a size larger than 2 cm-75 patients (74.3%). To establish whether tumor size can be a prognostic factor, patients were divided into two groups- 30 patients (23.7%) non-metastatic and 100 patients (76.3%) with metastases. It was established that in patients without metastases 42,3% have tumor less than 2 cm, 17.3% of them were with tumor more than 2 cm. In the group of patients with metastases 57.7% were with a tumor less than 2 cm, 82.7% of the patients were with tumor equal to or larger than 2 sm. Statistically significant correlation was found between the two groups of tumor size (p = 0,016). It is lead to an issue that the patients with tumor equal to or greater than 2 cm have significantly higher incidence of metastatic process.

According to the grade of malignancy (G) it is establishes the frequency of G1 is 6,1% (8 patients); G2 is 87.0% (114 patients); G is indeterminate in 6.9% (9 patients). G1 in patients without metastases is 0%, G2-3 is 77,4%; G indefinite is 22.6%; G1 in patients with metastases is 8,8%, G2-3 is 78, 0%; G indefinite is 13.2%. (p=0,121). Analyzing the relationship between Stern and frequency of malignancy in organ metastasis was found that in patients without visceral metastases G1 is 5,5% G2-3f 89,0% G indefinite was 5.5% at 1 or more organ metastases G1 is 6,9%; G2-3 is 84,5%; G can be found e 8,6%. Predominated patients are with moderate to low grade (p = 0,054).

Patients had examined the total number lymph nodes taken during the operation and the number of them with metastases. The t number of examined lymph nodes was 10.34 (+/–3.734). Minimum number tested in surgery lymph nodes was 1 and the maximum was 26. The average number of affected lymph nodes was 2,39 (+/–3,433); (p <0,0001). It was found that in 57.6% of patients with metastases in the lymph node 1, and 42.4% have more than 1 metastatic lymph node. The group of non-metastatic patients had 71.0% of 1 or less nodes and 29.0% more than 1 LN. In the group with metastatic disease were 52.9% of patients with lymph node 1, 47.1% - more than one affected lymph node. (P = 0,093). In the process of follow up relationship between the frequency of organ metastasis and number of involved lymph nodes were found: patients without organ metastasis were 49.3% without metastases in lymph nodes and 50.7% of metastases in one or more lymph nodes, in patients with organ metastasis 36,7% without lymph node metastasis and 63.3% of metastasis is 1 or more nodes.

From the followed up 100 patients with metastatic triple negative cancer 58% of them have organ metastasis, 33% have metastasized to other organs (local recurrence or brain), 28% have bone metastases and 11% are with metastases in the other breast .The patients suffered tumor with size in 2 cm without visceral metastases were 65.4%, and with tumor equal to or larger than 2 cm were 52.0%, patients with tumor less than 2 cm r with visceral metastases were 34.6% and p tumor > / = 2 cm with visceral metastases were 48.0%.

Distributed on the base of the stage of the illness patients with metastatic triple-negative breast cancer were divided into: S.T1N0M0-16,67%; T0-3N0-1M0-56,25%; T-3N2M0-21, 88%; TvsyakoNvsyako M1-5 , 21%.

In tracking data from ongoing adjuvant chemotherapy it was found that in 100 metastatic patients 60.2% were held adjuvant anthracycline chemotherapy, 19.4% were taking combination adjuvant chemotherapy with anthracyclines and taxane and 20.4% did not receive any adjuvant chemotherapy. Followed up DFS in the group taking combination adjuvant chemotherapy was 36 (+/–16.1) months in the group with adjuvant anthracycline chemotherapy alone was 27.5 (+/–26.6) months, and in the group without adjuvant hichmioterapiya-26 (+/–23.6) months. (p = 0,943). Comparing patients muzhdu held or naive ustatonvyava adjuvant chemotherapy is that patients with chemotherapy DFS is 33,6 months, and in patients with no chemotherapy was 30.0 months .The average DFS was 32.76 (+/–24.083).

When performing a first-line chemotherapy is reported PFS: the group with chemotherapy was PFS10,0-12,0 months. The patients conducted the first Limnia combination of Paclitaxel + Bevasizumab have PFS 9,35 month.

In a view of clarification of the molecular characterization of metastatic triple-negative tumors, were found the following frequency traced panel of 7 molecular markers:

1/Caveolin (CAV) it is found that is positive in 83.9% of patients and was negative at 9.7%., At 6.45 % can not be determined.

2/Ki67- it is found that at 16,4% expresses over 10%, 34.48% is negative, while the rest part is less than 10% expressed.

3/CK5/6-v 64.5% of the patients are positive for the basal cytokeratins, 12.9% were negative and 22.58% were undetermined.

4/CK14-is positive in o 61.29%, 25.81% area negative and 12.9% can not be determined.

5/VGFR- in 35.48% of patients was positive, in 54.84% was negative and in 9.68% could not be determined.

6/EGFR-in 32.26% was positive , in 61.29% was negative and in 6.45% could not be determined.

7/AR- 41.94% of the patients were positive 48.39% were negative and in 9.68% could not be determined.

Patients were divided into 2 groups with long and short DFS. Comparable to the frequency of CAV and AR . It was found that women with a short DFS in 65.0% with megative CAV quality. The group of patients with long DFS is 65% were positive for CAV. It that patients with a good prognosis with positive values of CAV. The group with low DSF is 45% were positive AR and the group with long DFS is 25% negative AR.

Were investigated 10 patients with BRCA1 mutation frequency of 7 molecular markers. Results show the following: CAV-38, 4% positive a; AR- 30% positive; CK5/6- 30% positive a; CK14- 40% positive ; EGFR -80% positive; VEGFR-40% positive,Ki67- 40% over 10%.Clinically significant is the value of EGFR (p=0,015).

Discussion

Our analysis of the patients with metastatic triple-negative breast cancer found that the tumor occurs most often in age of pre- and menopause. The predominant histological type was invasive ductal carcinoma. Tumor size equal to or larger than 2 cm had a higher frequency of metastatic process. Tumors larger than 2 cm have more common metastases even in one lymph node , which increases the risk of metastasis. The predominant grade is moderate to low differentiated types. The process of development of organ metastases dominates s, which is connected with poorer prognosis. Receiving adjuvant chemotherapy improves DFS. The longest DFS is found in patients with combine adjuvant anthracycline and taxane therapy. Applying of first-line chemotherapy with a taxane and Bevazisumab, for the metastatic disease lead to the satisfactory effect achieved in terms of PFS. Side effects requiring discontinuation of the therapy were not being pointed. As prognostic markers can be used the values of basal cytokeratines, Caveolin, and according to the expression of AR could be judged for the prognosis of metastatic disease and should be used as markers for susceptibility to antiandrogen therapy.

Conclusions

In conclusion, reviewing our data we were able to confirm that the TNBC is aggressive disease with a distinct pattern of recurrence. This pattern is characterized by

a rapidly raising rate of recurrence within the first 3 years after the diagnosis and by a decline in a recurrence risk after 5 years from the diagnosis. Given that fact and the high risk of visceral metastases, these breast cancer patients may require closer surveillance in the initial years of the follow-up. However, the hypothesis that earlier detection and aggressive therapy of metastatic recurrence could improve survival needs to be demonstrated. Current results illustrate the need to develop novel therapeutic alternatives for this subgroup of patients.

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