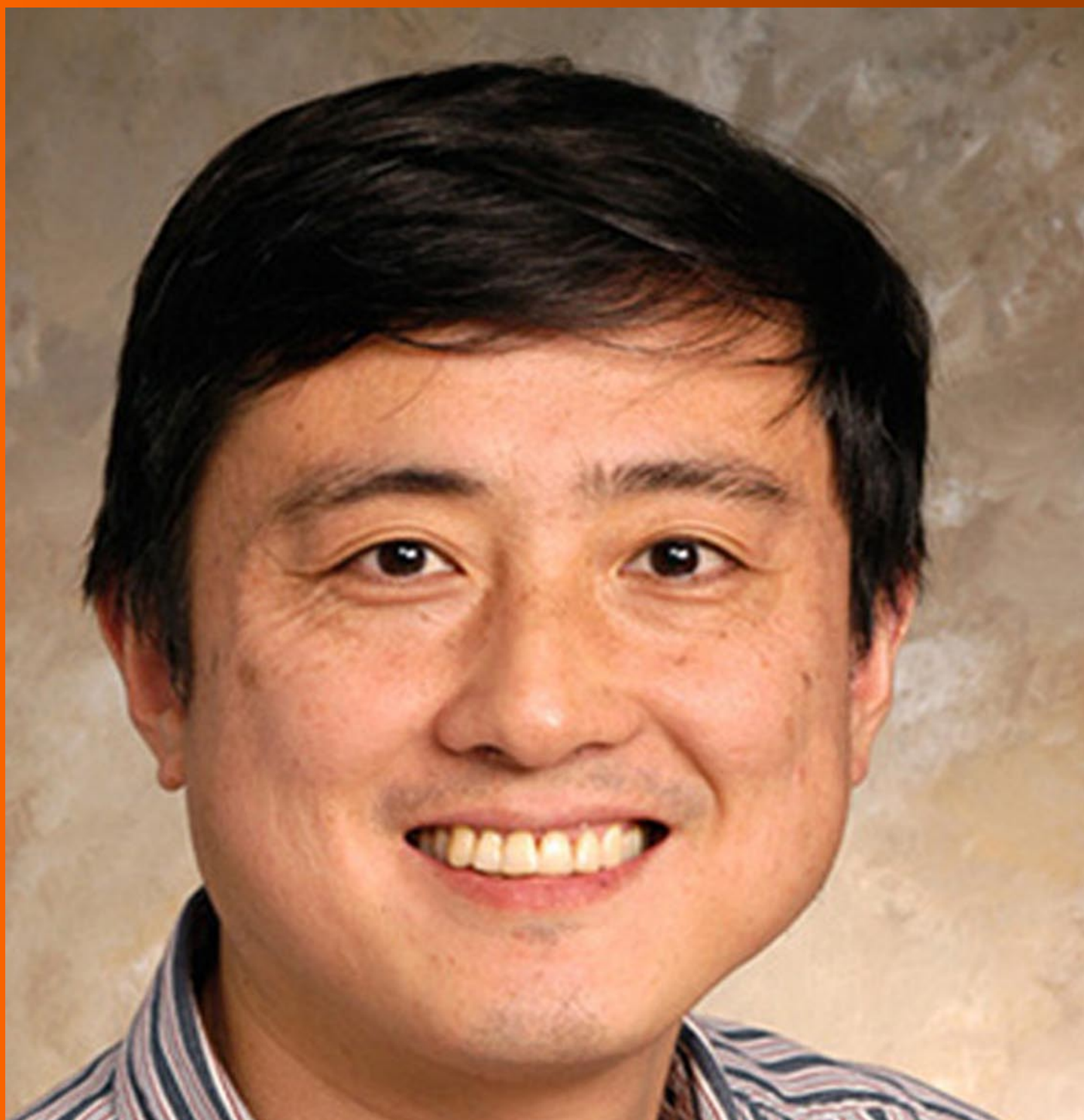


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## Transcranial Doppler ultrasonography: From methodology to major clinical applications

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### Abstract

Non-invasive Doppler ultrasonographic study of cerebral arteries [transcranial Doppler (TCD)] has been extensively applied on both outpatient and inpatient settings. It is performed placing a low-frequency ( $\leq 2$  MHz) transducer on the scalp of the patient over specific acoustic windows, in order to visualize the intracranial arterial vessels and to evaluate the cerebral blood flow velocity and its alteration in many different conditions. Nowadays the most widespread indication for TCD in outpatient setting is the research of right to left shunting, responsible of so called "paradoxical embolism", most often due to patency of foramen ovale which is responsible of the majority of cryptogenic strokes occurring in patients younger than 55 years old. TCD also allows to classify the grade of severity of such shunts using the so called "microembolic signal grading score". In addition TCD has found many useful applications in neurocritical care practice. It is useful on both adults and children for day-to-day bedside assessment of critical conditions including vasospasm in subarachnoid haemorrhage (caused by aneurysm rupture or traumatic injury), traumatic brain injury, brain stem death. It is used also to evaluate cerebral hemodynamic changes after stroke. It also allows to investigate cerebral pressure autoregulation and for the clinical evaluation of cerebral autoregulatory reserve.

**Key words:** Transcranial Doppler ultrasonography; Lindegaard ratio; Paradoxical embolism; Microembolic signals; Middle cerebral artery; Patent foramen ovale; Cryptogenic STroke; Vasospasm; Acute subarachnoid



hemorrhage; Ischemic stroke

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**Core tip:** Non-invasive Doppler ultrasonographic study of cerebral arteries [transcranial Doppler (TCD)] has been extensively applied on both outpatient and inpatient settings. Nowadays the most widespread indication for TCD in outpatient setting is the research of right to left shunting, responsible of so called "paradoxical embolism", most often due to a patency of foramen ovale which is responsible of the majority of cases of cryptogenic stroke occurring in patients younger than 55 years old. In addition TCD has found many useful applications in neurocritical care practice. It is useful on both adults and children for day-to-day bedside assessment of critical conditions including vasospasm in acute subarachnoid hemorrhage, traumatic brain injury, brain stem death.

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## INTRODUCTION

Non-invasive Doppler ultrasonographic study of cerebral arteries [transcranial Doppler (TCD)] was introduced in clinical practice in 1982<sup>[1]</sup>, since then it has been extensively applied in both outpatient and inpatient settings.

TCD ultrasonography is performed placing a low-frequency ( $\leq 2$  MHz) transducer on the scalp of the patient, in order to visualize the intracranial arterial vessels through specific acoustic windows, where bone is thinner, and evaluate cerebral blood flow velocity (CBFV) and its alteration in different cerebrovascular diseases and traumatic brain injuries.

It is inexpensive, repeatable, and can be used in neurocritical intensive care to continually monitor CBFV at bedside<sup>[2]</sup>.

Nowadays the most widespread indication for TCD in an outpatient setting is the research of right to left shunting (RLS), responsible of so called "paradoxical embolism", most often due to a patency of foramen ovale, mostly occurring in people younger than 55 years of age<sup>[3,4]</sup> with ischemic stroke or TIA of unknown origin.

For this purpose it is necessary to inject an ultrasonographic contrast medium in an upper limb vein. The finding of typical artifacts in middle cerebral artery (MCA) Doppler tracing after a provocative manoeuvre is diagnostic for RLS.

In addition TCD has found many useful applications in neurocritical care practice. In particular, its principal use is in the assessment of vasospastic reaction after subarachnoid haemorrhage<sup>[5]</sup> (caused by aneurysm rupture or traumatic injury)<sup>[6,7]</sup>, both in adults and children. It is used also to evaluate cerebral hemodynamic changes after stroke. Moreover TCD is able to provide a non-invasive estimate intracranial pressure (ICP) and to study cerebral autoregulatory function, thus helping to adjust cerebral perfusion pressure and mechanical ventilation in the single patient. Finally it represents an adjunctive test for the confirmation of brain death.

In this review we will describe in the first place physical principles, scanning proceedings, acoustic windows used in standard TCD examination, then will be discussed flow indices most frequently used in clinical practice. Finally we will focus on the incremental diagnostic role of TCD in Cryptogenic Stroke and the main critical care indications for this imaging modality.

## ANATOMY OF MAIN INTRACRANIAL ARTERIES

For better understanding of TCD findings and its applications in clinical setting, can be useful to make a brief description of the anatomy of intracranial arteries of major clinical interest: Internal carotid artery (ICA), MCA, anterior cerebral artery (ACA) and posterior cerebral artery (PCA).

The ICA, together with the external carotid artery is the terminal branch of the common carotid artery. It starts at C3 and C5 vertebral level, and it has been subdivided into seven segments (named from C1 to C7): (1) cervical segment; (2) petrous (horizontal) segment; (3) lacerum segment; (4) cavernous segment; (5) clinoid segment; (6) ophthalmic (supraclinoid) segment; and (7) communicating (terminal) segment. The ICA gives rise to two terminal branches which are the MCA and the ACA.

The MCA is the most frequently insonated artery during TCD examinations. It arises from the ICA and runs into the lateral sulcus where it then branches and gives blood to many parts of the lateral cerebral cortex. It can be subdivided into 4 tracts. The sphenoidal segment, M1 is also called the horizontal segment, because of its origin and its lateral course on sphenoid bone. The insular segment, M2 segment, is situated anteriorly on the insula. The opercular segments, M3 segment, extend laterally and exteriorly from the insula towards the cortex. The Cortical segments, the M4 terminal segments, irrigate cortex.

The ACA is smaller than MCA, and arches antero-medially to run anterior to genu of the corpus callosum, where the artery divides into its two major branches, pericallosal and callosomarginal.

The PCA represents the terminal branches of the basilar artery (BA) and irrigate the occipital lobes and posteromedial temporal lobes.

## PROBE AND SCANNING PROCEDURES

In clinical practice the most frequently used transducer is a pulsed Doppler sectorial probe with a 2.0-3.5 MHz emission frequency capable of changing the size of the sample volume in order to adapt to the diameter of major intracranial arteries, moreover the angle and position of insonation should be adjusted to provide/determined the highest quality Doppler signal.

The probe can then be fixed to the scalp with a headband so that the same angle of insonation for continuous flow velocity recordings is maintained throughout the exam. TCD can be conducted using two acquisition modalities.

The first is transcranial color-coded duplex sonography (TCCS), in which it is displayed a two-dimensional color-coded image<sup>[8]</sup> and, once the desired blood vessel is insonated, blood flow velocities may be measured using PW Doppler.

The second method is conventional TCD, using only Doppler probe function. The TCDS with combined ColorFlow and power Doppler provides more useful data than TCD since it allows direct imaging of the intracranial arteries, their anatomic course, diameter and relationships with the adjacent structures. Although the use of TCCS can be considered superior to TCD, no substantial differences were found when the two methods were compared in their accuracy to detect vasospasm in the setting of acute subarachnoidal haemorrhage (SAH)<sup>[1,9]</sup>.

In order to get a better quality of the Doppler signal in spite of background noises, the TCD devices are equipped with a larger sample volume compared to other PW Doppler probe. Specific Doppler settings used in TCD examination include also the emission power between 10 and 100 mW/cm<sup>2</sup> second and a pulse repetition frequency (PFR) up to 20 kHz with a focus depth between 40 and 60 mm<sup>[10]</sup>.

In clinical practice can be found two channel TCD transducers with dual emission frequency (2.0 MHz and 2.5 MHz, Embo-Dop). In standard TCD examination should be recorded bilateral PW-Doppler tracing lasting at least 10 cardiac cycles after a 30-s stabilized recording period.

## ACOUSTIC WINDOWS AND SCANNING PLANE

The transmission of an ultrasound beam through skull is influenced by structural characteristics of the diploe bone: The almost complete absence of bone spicules makes penetration of the ultrasound similar to conventional "acoustic windows" consenting the visualization of intracranial vessels. First of all the patient should be lying in supine position, with his head and shoulders on a pillow.

In general terms transcranial United States study is performed using two main scanning planes: The axial and coronal planes at a depth that allows to display also the contralateral vessels (14-16 cm depth), with the

brain stem structures remaining in the middle of the scanning plane.

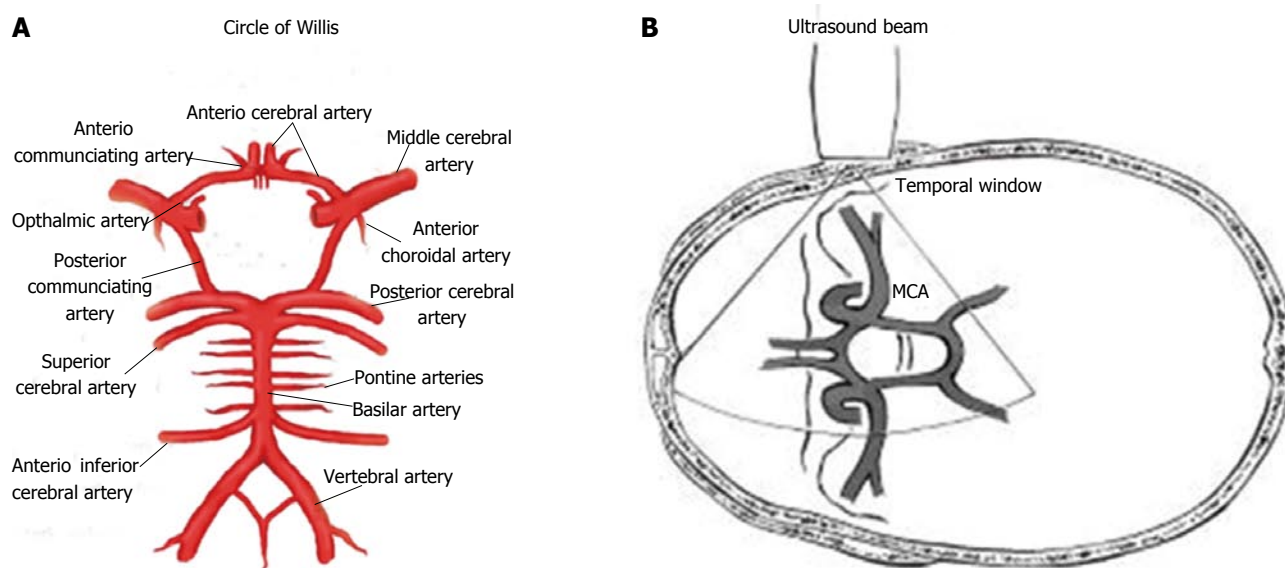
The axial scan is the one most commonly used and it allows two different types of imaging planes: The mesencephalic and diencephalic views. The mesencephalic plane is obtained by positioning the probe parallel to the zygomatic arch. At this level can be identified the hypoechogenic "butterfly-shaped midbrain", located about half of the scanning plane. In the 75% of cases, can be also detected the posterior communicating arteries if they have enough relevant diameter. In the middle of the diencephalic plane, which is obtained by slightly tilting the transducer 10 degrees upwards, can be seen the III ventricle: Behind it can be identified hyperechogenic pineal gland, while the thalamus and internal capsule are located anteriorly to it. The lateral ventricles can be also detected.

The coronal scan is obtained by rotating the probe of 90° from the axial position. In this view are shown the III ventricle, the lateral ventricles, the thalamus and internal capsule. The examination carried out on this plane is mainly useful for assessment of the shift of the median line caused by space occupying lesions (ischaemic area, haemorrhage and tumors). For what concerns the Doppler Study of Intracranial arteries, in clinical practice there are four acoustic windows that can be used for TCD and TCDS.

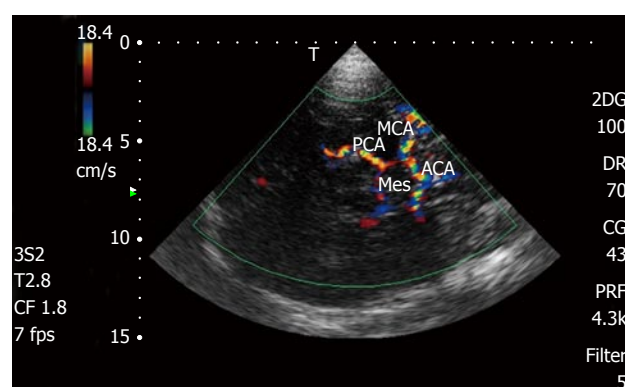
The temporal window is situated above the zygomatic arch, anterior to the tragus, using an axial plane in order to obtain a mesencephalic view, with the patient's head in the antero-posterior position (Figure 1). This window can be divided in an anterior, middle and posterior zone and allows to identify the MCA, in particular M1 and M2 tracts. From this approach can be also visualized A1 segment of the ACA, P1 and P2 segments of the PCA and C1 segment of the carotid siphon (CS) (Figure 2). In this temporal view can be also seen the communicating arteries - anterior and posterior - and the distal end of the BA. It should be noted that about 10%-20% of subjects have poor and unsuitable trans-temporal acoustic views, depending on patient age, female sex, and other factors affecting the temporal bone thickness<sup>[2,11,12]</sup>.

In the occipital window, the probe must be positioned on the median sub-occipital line and the patient should be sitting or lying down with the head turned to opposite direction respect to the operator with the chin lowered toward the shoulder. With US beam passing through the foramen magnum in this window it can be visualized the intracranial segment of the two vertebral arteries (VA) and the basilar trunk. All these three vessels dispose in a Y shape with their flow, depicted in blue color, moving away from the probe. In this view, with slight lateral movements it is possible to display also both the inferior cerebellar arteries, the posterior and the anterior<sup>[13]</sup>.

When TCD examination is performed from the orbital window, transducer is put perpendicularly to the eyelid, with patient's eye closed and looking on the opposite side respect to the probe. This approach allows to insonate



**Figure 1** Circle of Willis and Ultrasonographic study by transcranial Doppler ultrasound. A: Circle of Willis; B: Transmission of ultrasound beam through skull using pulsed Doppler sectorial probe with a 2.0-3.5 MHz emission frequency. Probe is positioned on temporal window. MCA: Middle cerebral artery.



**Figure 2** Transcranial Doppler color Doppler study of intracranial arteries. MCA: Middle cerebral artery; PCA: Posterior cerebral artery; ACA: Anterior cerebral artery; Mes: Mesencephalon.

the ophthalmic artery and the C2, C3 and C4 segments of the carotid syphon, through the foramen of the ocular cavity. The limitation of this approach is represented by the potential retinal injuries caused by the US beam: It is advisable to reduce 10%-15% power of the device respect to transtemporal scan.

In addition to the above mentioned views it can be also used the submandibular window, putting the transducer underneath the angle of the mandible, in front of the masseter muscle, inclinating the probe toward the skull. This window allows only the detection of the terminal segment (C5-C6) of the ICA (CI) and of the C1 segment of the CS. So, this approach is employed in case of impossibility to realize the TCD examination using the other standard windows for hemodynamic assessment of the Circle of Willis.

### MCA

The most frequently examined intracranial vessel in clinical practice is the MCA, it is easily delineated through

the temporal window above the zygomatic arch. The 60%-70% of the ICA blood flow is directed to MCA, so its TCD evaluation can be taken to represent almost total blood flow to ipsilateral hemisphere. MCA is detected at a depth of 45-60 mm, and the blood flow is directed toward the probe<sup>[14]</sup>. The identification of the sphenoid bone, through the "butterfly wing sign", leads to a easy MCA visualization in almost all patients, with a constant depth of  $59 \pm 3$  mm<sup>[15]</sup>. The time to achieve an adequate echographic image of MCA is about  $50 \pm 20$  s<sup>[15]</sup>.

## TCD: PHYSICAL PRINCIPLES AND TCD INDICES

TCD examination, as explained above, is executed placing on the surface of the skull a probe of a range-gated ultrasound Doppler instrument, which allows to determine flow velocities in the intracranial arteries<sup>[16]</sup>. The attenuation of US beam due to bone and soft tissues requires a low emission frequency in order to provide satisfactory recordings of intracranial CBFVs, usually a 2-MHz frequency is adopted<sup>[16]</sup>.

In physical terms, the probe trasmits an ultrasonic beam that crosses the skull and is reflected back from the erythrocytes flowing in blood vessels, when a sound wave hits a moving object, the wave of reflection shows a shift in its frequency (the Doppler shift  $f$ ) that proportionally correlated to the velocity ( $V$ ) of the same object. The Doppler shift represents the difference between the transmitted and received signal frequency while the time interval from pulse emission and reception determines the depth at which any Doppler frequency shift is detected<sup>[16]</sup>.

In the intracranial vessels, as in the arteries of other vital organs (liver, kidney, and heart), the Doppler signal shows a prominent diastolic component of blood flow.

The following equation derived from Doppler pri-



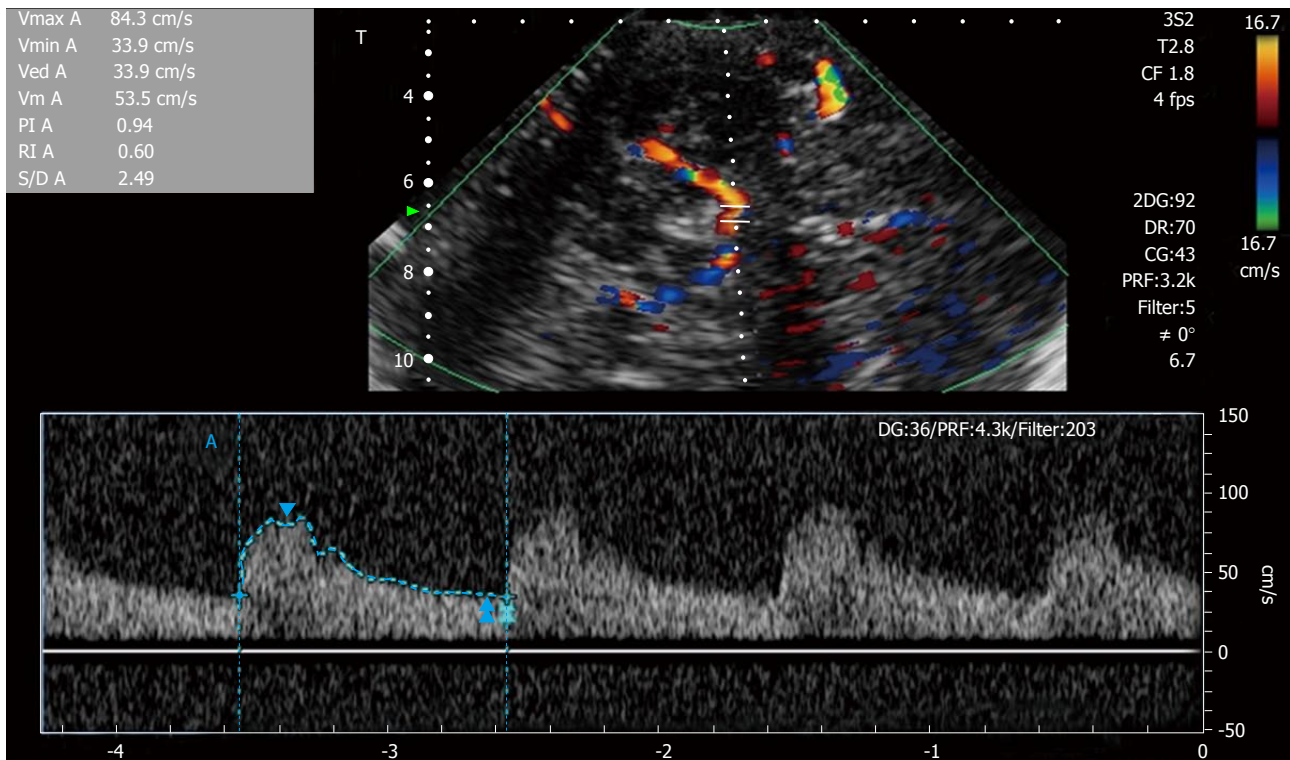


Figure 3 Transcranial Doppler spectral Doppler study of intracranial middle cerebral artery.

nciples described above, is used for estimation of CBFV with TCD:

$$v = [(c \times f)/(2 \times fo \times \cos\theta)]$$

Where  $c$  represents the speed of the US Wave emitted from probe,  $fo$  represents the emitted Wave pulse frequency,  $\theta$  represents the angle of formed by reflected wave relatively to the initial US emission beam<sup>[17]</sup>.

When performing the TCD examination the operator should keep a Theta angle of 15° or less, because the cosine remains 0.96 or more so that any error caused by changes in the angle is less than 4%.

Mean CBFV is derived through the spectral envelope of Doppler Signal, as indicated by following formula:

$$\text{Mean CBFV} = [\text{PSV} + (\text{EDV} \times 2)]/3,$$

Where PSV is peak systolic velocity, and EDV is end-diastolic blood flow velocity<sup>[18,19]</sup> (Figure 3).

By the Bernoulli principle, the correlation between velocity and pressure exerted by blood flowing, is characterized by a decrease of pressure exerted by the fluid as the velocity of flow increases. Moreover, it should be remembered that by the continuity principle the CBFV in a given artery is inversely related to the cross-sectional area of the same artery<sup>[19,20]</sup>. So, TCD gives an indirect evaluation of the diameter of intracranial vessel through the analysis of blood flow velocity<sup>[19]</sup>. It should be also considered that there are many physiologic factors affecting CBFV: Age, hematocrit, gender, fever, metabolic

factors, pregnancy, menstruation, exercise, and brain activity<sup>[21-24]</sup> (Tables 1 and 2).

In clinical practice an higher mean CBFV is suggestive of hyperdynamic flow, stenotic arterial disease or vasospastic reaction. On the other hand, a decreased value of this parameter could be suggestive of low intracranial perfusion pressure, or increased ICP or even brain stem death<sup>[21]</sup>. Stenosis or vasospasm in an arterial segment is defined as an increase in mean CBFV of more than 30 cm/s, within a tract 5 to 10 mm long on one side, if confronted with the healthy corresponding contralateral arterial tract<sup>[25]</sup>.

The Lindegard ratio (LR) permits to differentiate between hyperdynamic arterial blood flow and vasospasm. It is obtained by the following equation:

$$\text{LR} = \text{MCA mean CBFV/extracranial ICA mean CBF-V}^{[26]}.$$

This ratio tends to increase in relation to the severity of symptomatic vasospasm (VSP). Normal reference range is from 1.1 to 2.3 and in the absence of vasospasm is lower than 3<sup>[26]</sup>. When the CBFV is elevated but the LR ratio is lower than 3, the elevation is considered to be caused by hyperemia, because patients after acute subarachnoidal haemorrhage (aSAH) are often treated following so called triple-H therapy: Hypertension, hypervolemia, hemodilution. In case of a ratio more than 6, there is a severe VSP<sup>[20,27,28]</sup>. So, in summary, LR defines the severity of vasospasm: MCA mean CBFV/extracranial ICA mean CBFV > 3 mild to moderate VSP; MCA MEan CBFV/extracranial ICA mean CBFV > 6 severe VSP.

**Table 1** Factors influencing cerebral blood flow velocity

Factor change in CBFV	
Age	Increase up 6-10 yr then decrease
Sex	Women > men
Pregnancy	Decrement in the III Trimester
Hematocrit	Increase with decreasing Hct
PCO <sub>2</sub>	Increase with increasing PCO <sub>2</sub>
Main	Arterial pressure increase with increasing MAP

CBFV: Cerebral blood flow velocity; MAP: Mean arterial pressure.

**Table 2** Mean cerebral blood flow velocity (cm/s) related to age

Artery	Age 20-40 yr	Age 40-60 yr	Age > 60 yr
Anterior cerebral artery	56-60	53-61	44-51
Middle cerebral artery	74-81	72-73	58-59
Posterior cerebral artery P1	48-57	41-56	37-47
Posterior cerebral artery P2	43-51	40-57	37-47
Vertebral artery	37-51	29-50	30-37
Basilar artery	39-58	27-56	29-47

Moreover, for detecting the severity of BA vasospasm it is calculated the modified LR: BA mean CBFV/left or right extracranial VA Mean CBFV; LR modified: 2 to 2.49 possible VSP; LR modified: 2.5 to 2.99 moderate VSP; LR modified: > 3 severe VSP (Table 3).

### Incremental diagnostic role in cryptogenic stroke

The American Academy of Neurology states that TCD main clinical indications include ischaemic cerebrovascular disease, neurointensive care and periprocedural applications in the setting of carotid and intracranial vascular interventions<sup>[29]</sup>.

In this section we shall focus on the role of TCD ultrasonography for the research of the so-named "paradoxical embolism" through patent foramen ovale (PFO) which has been recognized as a relevant aetiological factor for cryptogenic stroke, mainly when occurring in patients younger than 55 years old<sup>[30,31]</sup>. In fact TCD can be used to detect a cardiac source of embolism due to right-left intracardiac or pulmonary shunts (*e.g.*, patency of foramen ovale or pulmonary arterio-venous malformations). It also allows to classify the grade of severity of such shunts using the so called "microembolic signals (MES) grading score"<sup>[32,33]</sup>.

## PARADOXICAL EMBOLISM: PFO AND CRYPTOGENIC STROKE

PFO can be considered a remnant of the fetal circulation. During the fetal life, it allows the transit of blood flow from the right cardiac chambers to the left cardiac chambers, determining a so-called right-left shunt. The presence of a PFO in adult life can be considered persistence of such fetal communication between right and left atrium, it usually appears as an oblique, slit-shaped defect which looks like a tunnel. The cause of its incomplete closure

**Table 3** Intracranial arteries: Severity of vasospasm

	MFV (cm/s)	LR	LR modified
MCA or ICA vasospasm			
Mild (< 25%)	120-149	3-6	
Moderate (25%-50%)	150-199	3-6	
Severe (> 50%)	> 200	> 6	
BA vasospasm			
Possible vasospasm	70-85		2-2.49
Moderate (25%-50%)	> 85		2.5-2.99
Severe (> 50%)	> 85		> 3

MCA: Middle cerebral artery; ICA: Internal carotid artery; LR: Lindegaard ratio; BA: Basilar artery; MFV: Mean flow velocity.

after birth is not known, but it appears to be associated with multifactorial inheritance. In some patients such interatrial communication can be associated with a thinner and redundant interatrial septum which shows mono or bidirectional movement during cardiac cycle [atrial septal aneurysm (ASA)].

Frequency of such lesion in general adult population varies between 25% to 30%: The prevalence and size of the defect are similar for males and females<sup>[33-35]</sup> and decrease progressively with age. In detail, PFO is diagnosed into 34% of patients 30's old, into 25% between 30's and 80's old, and finally into 20% over 80's old and this trend is inversely related to the dimensions of the defect. Moreover the average dimensions increase progressively from 3.4 mm in the first decade of life, to 5.8 mm after the ninth decade<sup>[36]</sup>. The explanation of this phenomenon is probably that larger defects tend to persist while those of smaller dimensions go towards spontaneous closure with time<sup>[36]</sup>.

Most individuals with a PFO remain asymptomatic, but in some cases it has been associated with several clinical manifestations due to transient RLS, such as decompression sickness in scuba divers<sup>[37]</sup> or platypnea-orthodeoxia syndrome<sup>[38]</sup>. But, the most important potential manifestations related to PFO are represented by cryptogenic stroke due to paradoxical embolism, and migraine and vascular headache, although the causal relationship between PFO and migraine is not yet completely understood and is still object of research.

The clinical significance and the pathogenic role of PFO in patients with cryptogenic stroke is still a matter of debate: About 40% of ischemic strokes that occur in people under the age of 55 are cryptogenic<sup>[31,39]</sup>. Cryptogenic stroke is defined as an ischemic stroke which takes place without any clearly identifiable etiology from cardioembolic source or large vessel atheromiasia. This kind of cerebrovascular accident has an embolic origin and typically shows a distribution pattern that is not consistent with small vessel involvement.

Prevalence of PFO is higher among subjects hit by a cryptogenic stroke: In a prospective study (the PFO-ASA study) were included 581 patients with a cryptogenic cerebrovascular ischemic accident of less than 55 years of age (mean 42), 37% had PFO and 9% had PFO associated with ASA<sup>[39]</sup>.



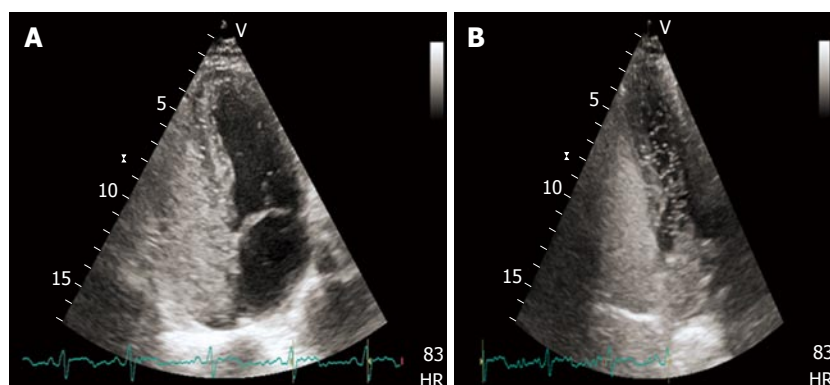


Figure 4 Transthoracic echocardiography showing high grade right to left shunt with evident micro-bubbles in the left heart after intravenous contrast administration (A and B).

In the PFO in Cryptogenic Stroke study was found an analogous prevalence of PFO (39%) in 250 patients with a mean age of 59 years<sup>[40]</sup>. Moreover patients with cryptogenic stroke showed significantly higher rate of a large PFO compared to patients with a stroke of known cause (20% vs 9.7%)<sup>[40]</sup>. The pathophysiological mechanism underlying stroke of cryptogenic origin in PFO carriers probably consists in a paradoxical embolism in the setting of a transient right to left shunt. In detail when the right atrial pressure is higher than the pressure in the left atrium, a transient right-to-left shunt possibly occurs through a PFO that becomes a pathway for the passage of emboli from venous to arterial circulation (paradoxical embolism).

Thus, a transitory occurrence of interatrial right-to-left pressure gradient can cause paradoxical shunting and can commonly be elicited using specific maneuvers in patients with no baseline RLS (including both subjects without net shunt at all or with a left-to-right shunt). In particular a short-lived right-to-left gradient can be present in normal individuals during early ventricular systole and after release of maneuvers which raise intra-abdominal pressure (such as Valsalva maneuver, defecation, cough, lifting or pushing heavy objects). In a community based study of 148 subjects carriers of a PFO, 57% showed resting right-to-left shunt, and 92% showed elicitable RLS after Valsalva maneuver or cough<sup>[41]</sup>. In summary PFO represents a possible cardioembolic source responsible of cryptogenic stroke and a risk factor for neurological events.

## ROLE OF THE TCD METHODOLOGY AND DIAGNOSTIC ACCURACY

The diagnosis of PFO, in order to achieve a clinical significance, should provide both an anatomic description and a physiologic assessment of a potential RLS. The first is usually obtained by transesophageal echocardiography (TEE) or by intracardiac echocardiography while the physiologic assessment of an RLS is usually obtained using contrast transthoracic echocardiography (TTE) or TCD. A definite ultrasonographic diagnosis of tem-

porary right-left shunting requires the use of contrast enhancement. In clinical practice the most frequently used ultrasonographic contrast medium is represented by agitated saline solution. In fact the different density present at the interface separating gas-containing micro-bubbles from surrounding tissue modifies the "acoustic impedance" of such interface: The higher impedance the higher echogenicity at the same level. Moreover gas microbubbles work very effectively as contrast medium, since they are 100000 times less dense than blood<sup>[42]</sup>.

Traditionally, TEE supported by agitated saline contrast-enhancement has always been considered the gold standard technique both for demonstration of a right-to-left shunt through a PFO and for morphological description of interatrial septum. It should be noted that micro-bubbles with a diameter smaller than 9  $\mu\text{m}$  are not able to pass through pulmonary capillary network, so the finding of any micro-bubble after intravenous contrast administration is diagnostic for RLS.

Contrast enhancement for the research of paradoxical interatrial shunting has been applied also to TTE (Figure 4), with a reported sensitivity and specificity similar to that of c-TEE<sup>[43,44]</sup>. This was also due to the introduction of harmonic imaging, which improved image quality of TTE<sup>[45]</sup>. In recent times contrast enhanced TCD (c-TCD) has gained a growing role for the diagnosis of transient RLS, which allows to recognize the passage of intravenously injected micro-bubbles directly in cerebral circulation. As stated above about TEE, also with c-TCD the finding of a single microbubble in cerebral arterial circulation (usually MCA) is considered diagnostic of RLS. C-TCD represents a low cost, widely available, non-invasive imaging technique, of easy interpretation, which also permits to semiquantitatively estimate severity of venous-arterial shunt<sup>[46]</sup>.

In order to highlight RLS a contrast medium, usually agitated saline is injected into a peripheral vein, usually right antecubital vein in three boluses, at the same time the Doppler signal is recorded while the patient performs a Valsalva maneuver. The contrast agent is obtained by combining 9 mL of normal saline solution with 1 mL of air and then it is usually shaken up about 10 times through a system constituted by two 10 mL syringes

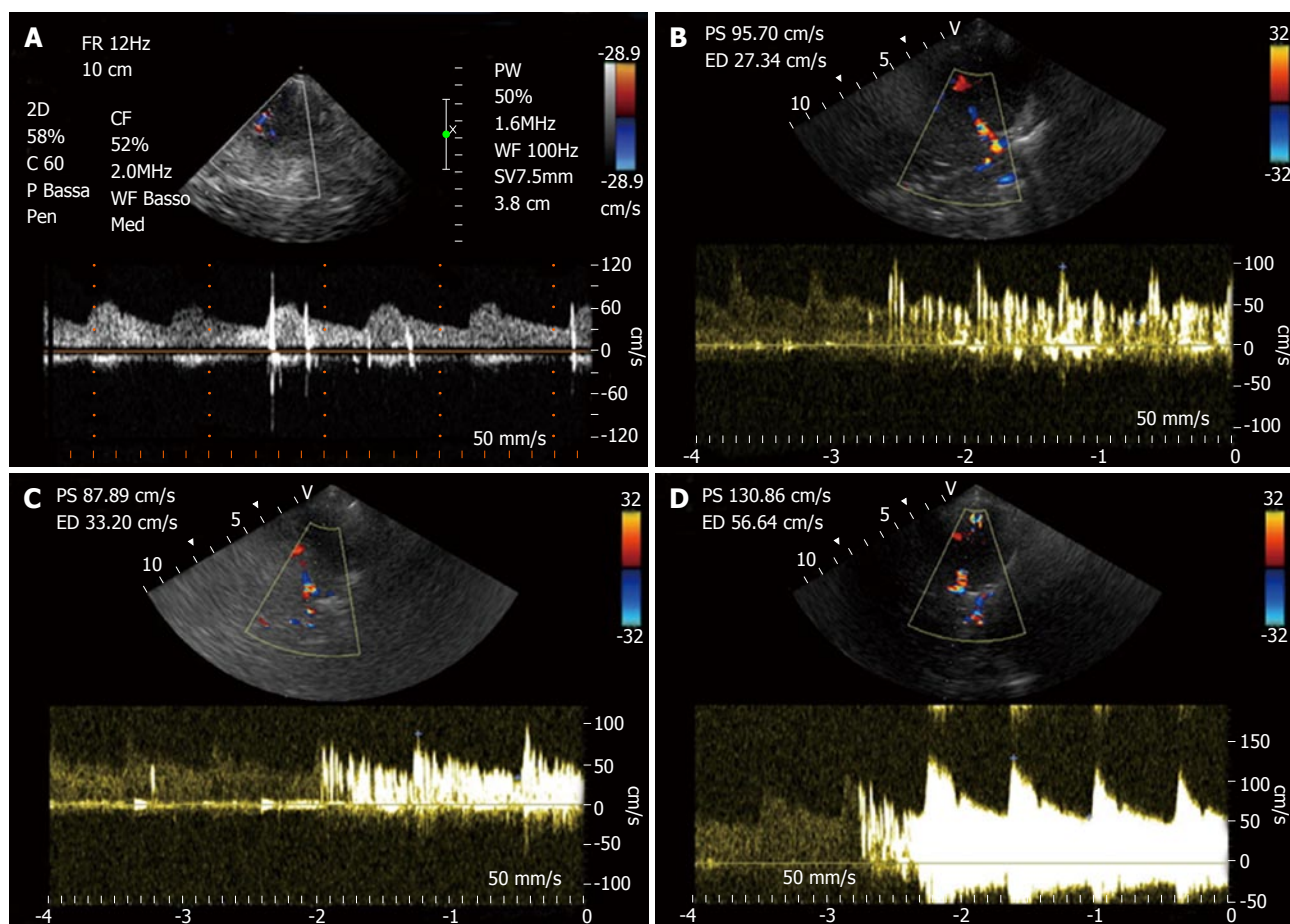


Figure 5 Right to left shunt with microembolic signals. A: Low grade shunt; B: Moderate grade shunt; C: High grade shunt (shower); D: Curtain effect.

Table 4 Grade of transient right to left shunting based on microembolic signals grading score

Grade transient shunt	MES
No shunt	0
Low grade shunt	1-10
Moderate grade shunt	11-25
High grade shunt	> 25 (shower) or uncountable (curtain effect)

MES: Microembolic signals.

linked by a 3-way stopcock. The agitated solution is then administrated into the antecubital vein by an 18-gauge. The patient is then invited to perform a forced expiration against the closed glottis for a minimum of 10 s (Valsalva Maneuver). When a right to left shunt is present the air microbubbles constituting ultrasonographic contrast medium will directly pass from venous to systemic circulation and will be visualized in cerebral arterial vessels as so called MES.

In addition it is possible to evaluate the entity and functional relevance of a paradoxical RLS through the MES grading score, based on the number of Doppler signals provoked by microbubbles that reach MCA (Figure 5 and Table 4). Moreover the entity of right to left shunt is directly associated with the risk of stroke<sup>[33,47]</sup>. It should be noted that when the number of microbubbles passing

through a RLS is very low, they may not be able to reach the MCA giving a false negative result of absent RLS. But on the other hand clinical relevance of such small entity of shunt is uncertain. A very large amount of microbubbles reaching MCA is responsible on the Doppler Spectrum of the so called "Curtain effect", characterized by impossibility to identify on Doppler spectrum a single MES. In the work of Serena *et al*<sup>[48]</sup>, "Curtain effect" is characteristically found in patient hit by cryptogenic stroke, so the identification of this Doppler aspect in a subject could denote a higher risk of cerebrovascular events, thus providing useful information for the clinician in order to differentiate "innocent" from "harmful" shunts information<sup>[48]</sup>.

Nowadays there is no consensus about a definite time interval from contrast administration until recording of the first MES on MCA Doppler spectrum. In a recent work, twenty-six patients with stroke (16 with PFO vs 10 without PFO, diagnosed by cTEE) after a positive cTCD test were evaluated for three parameters: The amount of MES, latency time (LT) before the first MES and the duration time of MES, looking for any difference between PFO carriers and no-PFO. The presence of more than 9 MES with a LT of less than 9 s (so called rule of nine) can be considered a marker for PFO diagnosis by cTEE, providing a specificity and positive predictive value (PPV) of 100%<sup>[49]</sup>.

**Table 5** Diagnostic role of transcranial Doppler and its accuracy

Ref.	No. of patients	Sensitivity (%)	Specificity (%)	Accuracy (%)	Cut-off for RLS
Serena <i>et al</i> <sup>[48]</sup> , 1998	55	100	100	100	≥ 1 MES <sup>1</sup>
Lange <i>et al</i> <sup>[49]</sup> , 2010	26	31	100	65.5	≥ 9 MES
González-Alujas <i>et al</i> <sup>[52]</sup> , 2011	93	97	98	97.5	≥ 1 MES
Mojadidi <i>et al</i> <sup>[51]</sup> , 2014	1968	97	93	95	Meta-analysis <sup>2</sup>

<sup>1</sup>In this study c-TCD performs better than c-TEE; <sup>2</sup>This study is a large meta-analysis comprising 27 studies. TCD: Transcranial Doppler; c-TCD: Contrast enhanced TCD; TEE: Transesophageal echocardiography; RLS: Right-to-left shunting; MES: Microembolic signals.

To increase the test sensitivity for identification of the right to left shunt [PFO detection can be increased by asking patient to cough or by releasing a sustained Valsalva manoeuvre (VM)] the patient may be asked to cough or to perform a prolonged VM, since in the release phase of these strain manoeuvres a RLS can be elicited when the right atrial chamber is filled with blood from the abdominal cavity, while the left atrial chamber is still volume depleted before passage of increased blood return through pulmonary circulation<sup>[50]</sup>. VM should be always performed for the research of RLS, it is started 5 s after agitated saline administration (because it represents the average time interval required for the injected solution to reach right atrium from the cubital vein).

Effectiveness of VM strength can be assessed through peak flow velocity of the MCA Doppler Spectrum, which tends to decrease during a well executed VM<sup>[44]</sup>. Mojadidi *et al*<sup>[51]</sup> have published an extensive bivariate meta-analysis of 27 prospective studies with a total of 1968 patients comparing PFO detection with TCD to the c-TEE as gold standard. Starting from these data they could determine sensitivity in FOP identification for TCD (index test) and TEE (considered reference test) according to type of contrast medium, different provocative manoeuvres, different quantitative microembolic cutoffs, different time of onset of provocation maneuver, and insonation of a single or both MCA. No difference in sensitivity and specificity was found between each contrast medium (agitated saline, Echovist, and gelatin-based solutions,  $P > 0.05$ ). No significant difference between cough or Valsalva as provocative maneuver was evident ( $P > 0.7$ ). When cut-off number of 10 microbubbles instead of 1 was chosen to define TCD positivity study specificity was showed a significant improvement from 89% to 100% ( $P = 0.04$ ), nevertheless this approach did not result in a substantial improvement in sensitivity (from 98% to 97%,  $P = 0.29$ ).

Duration of Valsalva strain, more or less than 5 s, did not show a significant influence sensitivity or specificity of TCD ( $P > 0.50$ ). Finally a not significant trend towards an improvement of specificity when a single MCA was insonated instead of both (95% specificity vs 89% respectively,  $P = 0.09$ ), while no significant difference was seen regarding sensitivity ( $P = 0.15$ ).

In conclusion Mojadidi found an overall sensitivity of 97% and a specificity of 93% for detection of RLS with c-TCD compared with c-TEE<sup>[51]</sup>. Increasing the number

of microbubbles needed for a positive TCD from 1 to 10 resulted in a predictable significant improvement in specificity. TCD showed a good diagnostic performance with an overall LR+ of 13.51 and LR- of 0.04 and a disease probability of 93%-94% after a positive test and of 4% after a negative test<sup>[51]</sup>.

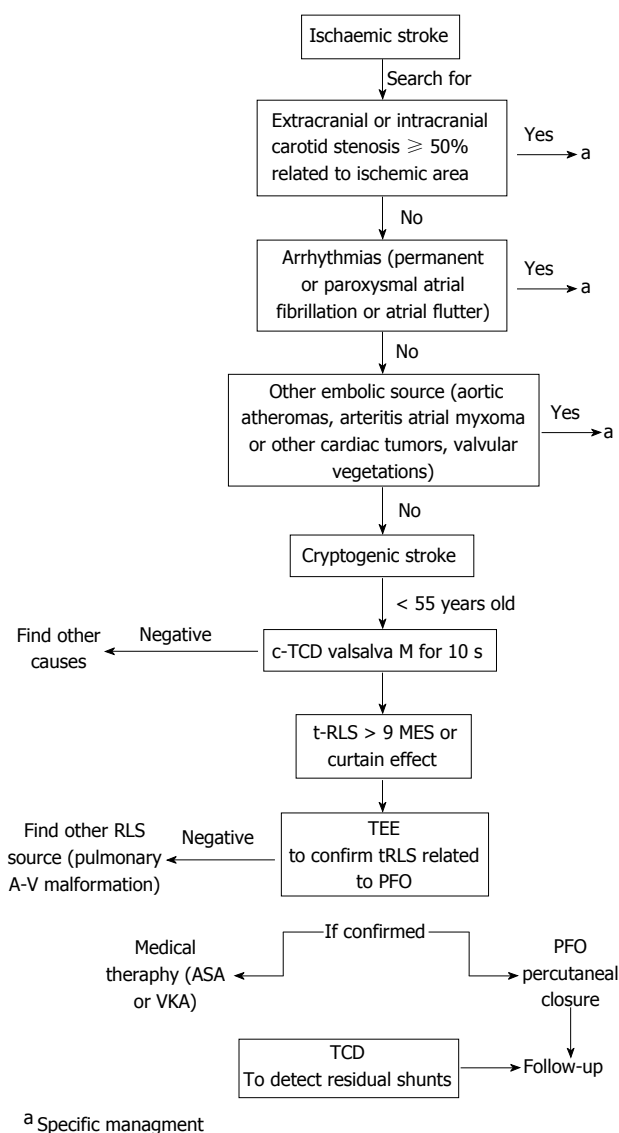
In Table 5 are summarized sensitivity, specificity and diagnostic accuracy of c-TCD for the research of RLS in patients with cryptogenic stroke in different studies, which adopted TEE as a gold standard. So in the context of a cryptogenic stroke, the clinician is called to choose the best diagnostic technique between c-TCD, c-TEE or c-TTE in order to detect a RLS.

TEE provides detailed morphological description of interatrial septum and is able to identify anatomic characteristics of a PFO. In particular a diameter greater than 4 mm or the coexistence of an aneurysm of interatrial septum is associated with recurrent ischaemic cerebrovascular accidents. These c-TEE may be useful in guiding management towards an interventional strategy instead antithrombotic treatment in patient hit by cryptogenic stroke<sup>[52]</sup>. On the other hand recent published data suggest that TEE should not be considered the true gold standard imaging technique for the detection of RLS. In fact in the case of really small shunts (of 1 to 3 bubbles), c-TCD may show a better sensitivity, because such a small number of microbubbles may be missed on a single tomographic echocardiographic plain<sup>[53]</sup>. Moreover TEE is an high cost, semi-invasive technique characterized by poor patient's compliance, it is not always available and contrast administration may be inconclusive or be followed by falsely negative results<sup>[53]</sup>, mainly due to inability of the patient to carry out an effective Valsalva maneuver<sup>[54-57]</sup>.

A lower sensitivity of c-TEE compared with c-TTE and c-TCD was reported by the work of González-Alujas *et al*<sup>[52]</sup> (86% sensitivity for TEE, vs 100% for TTE and 97% for TCD,  $P < 0.001$ ), while here was no significant difference in sensitivity between TTE and TCD. These results may have a clinical impact, because they confirm that TEE is not the most accurate diagnostic technique as it was commonly considered in the past years.

Higher sensitivity shown by c-TCD is also due to its positive results also in presence of extracardiac shunts, such as pulmonary arterio-venous malformations. TCD is not able to show the exact anatomic position of the RLS, although LT from contrast injection in antecubital





**Figure 6** Contrast enhanced transcranial Doppler as a first line screening tool in the setting of a cryptogenic stroke. TCD: Transcranial Doppler; c-TCD: Contrast enhanced TCD; TEE: Transesophageal echocardiography; RLS: Right-to-left shunting; PFO: Patent foramen ovale; ASA: Atrial septal aneurysm; MES: Microembolic signals; VKA: Vitamin K antagonist.

vein to the appearance of MES in the setting of an intracardiac shunt is about 11 s, while in presence of a pulmonary artero-venous malformation is about 14 s<sup>[58]</sup>. Interestingly as reported in the work of Gonzalez-Aluja<sup>[52]</sup>, c-TTE performed simultaneously with TCD was able to confirm presence of an artero-venous pulmonary malformation in a positive TCD, showing the entrance of microbubbles in left atrium from a pulmonary vein.

## RECOMMENDATIONS

American Academy of Neurology confers a class II indication for both c-TCD and TEE for interatrial shunt detection<sup>[29,58]</sup>. On the other hand Italian stroke guidelines (SPREAD) consider TCD a better screening tool than TEE in the population of patient with suspect shunt through a foramen ovale<sup>[59]</sup>.

In a consensus document published on behalf of Italian society of interventional cardiology by Pristipino *et al*<sup>[60]</sup> in 2010 TCD was proposed as first-choice screening tool for RLS in the setting of a cryptogenic stroke in subjects 55 years old or younger, while in patients older than 55 TEE was recommended as first-line test.

In conclusion our suggestion in the setting of a cryptogenic ischemic stroke is to use c-TCD as a first line screening tool, due to its higher sensitivity and its better tolerability. TEE may be considered as a complementary imaging technique for a more detailed anatomic definition of interatrial septum, especially when PFO closure is contemplated (Figure 6). Moreover TCD is also useful for follow-up of patients after PFO closure in order to identify those with residual shunting<sup>[61]</sup> due also to its repeatability and its sensitivity for the detection of small entity residual shunts<sup>[62]</sup>.

## Principal applications in neurocritical care unit

TCD examinations have gained an important role in the very early phase of critical cerebral pathologies, as well during follow-up of patients with chronic cerebrovascular diseases.

In neurocritical care bedside TCD examination provides the clinician useful information to guide the management of patients with SAH, allowing to recognize vasospasm both in adult and paediatric patients. Moreover TCD represents an additional non-invasive tool for cerebral hemodynamic monitoring, which is particularly of interest in the follow-up of patients with ischemic stroke. It allows to investigate cerebral pressure autoregulation and for the clinical evaluation of cerebral autoregulatory reserve<sup>[63]</sup>. TCD has important clinical application in the management of patients with sickle-cell disease, traumatic brain injury (TBI), brain stem death<sup>[64]</sup>, raised ICP<sup>[65]</sup>.

## VASOSPASM AFTER SAH: DIAGNOSIS AND MONITORING ON TCD

Symptomatic vasospasm (VSP) is a frequent complication of aSAH, secondary to intracranial aneurysm rupture (aSAH). It should be considered that 25% of patients affected by aSAH develops clinical delayed ischemic deficits due to vasospasm<sup>[6,11,66-68]</sup>.

The retarded vasospasm of intracranial arteries is reported by angiographic studies to occur in about 70% of patients affected by SAH and in most cases it develops between 4-17 d following the acute episode<sup>[20,69]</sup>. When it's still present up to day 20 by TCD<sup>[70]</sup>, morbidity and mortality are considered to increase significantly up to 20%<sup>[8,71,72]</sup>.

VSP is characterized by a decrease in blood flow through cerebral regions after aSAH secondary to reflex vasoconstriction of intracranial arteries<sup>[20]</sup>. The exact mechanism causative of delayed cerebral ischemia (DCI) is not clearly understood, and several theories have been proposed<sup>[73]</sup>. Clinically, the terms "delayed ischemic neurologic deficit and DCI" have been introduced to

describe symptomatic VSP.

Angiographic study is considered as the gold standard for the detection of intracranial vasospastic reaction but it is invasive diagnostic exam and cannot be used for continuous monitorization<sup>[2,74]</sup>. Angiographic VSP, identified by digital subtraction angiography and computed tomography angiography (CTA) has been diagnosed up to 50% to 70% of patients affected by aSAH and about half of them showed clinical symptoms<sup>[73,75]</sup>.

TCD ultrasonography is a noninvasive, repeatable, and relatively inexpensive imaging test and it could be used in patients affected by aSAH for diagnosing and monitoring of VSP<sup>[16,76]</sup>. It can identify cerebral hemodynamic changes, diagnosing VSP before appearance of clinical neurologic deficits, and can suggest earlier intervention<sup>[77]</sup>.

So, in NCCU daily TCD monitoring is warranted for the management of patient affected by aSAH: The timing of the development and resolution of VSP can guide therapeutic strategies such as triple-H therapy (hypertension, haemodilution, and hypervolaemia). TCD also can monitor the efficacy of interventional procedures such as transluminal balloon angioplasty<sup>[78]</sup> and can identify patients at higher risk of developing DCI.

TCD is able to recognize vasospastic reactions in MCA and BA with a good sensitivity and specificity. A systematic analysis collecting 26 works, which compared TCD with angiographic exam has shown that a Mean CBFV > 120 cm/s in MCA detected by TCD carries 99% specificity and 67% sensitivity for identification of angiographic vasospasm of  $\geq 25\%$ <sup>[79]</sup>. For MCA vasospasm it is calculated as MCA mean CBFV/extracranial ICA mean CBFV (Table 3). MCA mean CBFV/extracranial ICA mean CBFV > 3 indicates mild to moderate VSP. MCA mean CBFV/extracranial ICA mean CBFV > 6 indicates severe VSP. Thus TCD, compared with angiography as gold standard, showed high specificity and high PPV for MCA vasospasm detection, making it a very useful diagnostic tool in this setting<sup>[79]</sup>.

TCD criteria for BA VSP have not been universally defined yet (Table 3). Sviri *et al.*<sup>[75]</sup> argued that the CBFV ratio (LR BA/VA) between the BA and the extracranial VA is related to the degree BA narrowing ( $0.648$ ,  $P < 0.0001$ ). A BA/VA ratio (LR BA/VA) over 2.5 with BA velocity higher than 85 cm/s was 86% sensitive and 97% specific for BA narrowing of more than 25%. A BA/VA ratio over 3.0 with BA velocities higher than 85 cm/s was 92% sensitive and 97% specific for BA narrowing of more than 50%. The investigators so concluded that the BA/VA ratio increases the sensitivity and specificity of BA VSP diagnosis by TCD. Therefore, the reported evidences indicate that TCD is highly predictive of angiographically demonstrated VSP in the MCA, but its diagnostic accuracy is lower to identify VSP in the BA<sup>[80,81]</sup>. For VSP detection after aSAH in ACA and PCA territory, TCD's diagnostic performance has revealed quite insufficient. In a study involving 57 patients undergone TCD study within 24 h of cerebral angiographic exam, a mean CBFV superior to 120 cm/s in ACA showed a 18% sensitivity and 65%

specificity to detect VSP and a CBFV superior to  $\geq 90$  cm/s in PCA had 48% sensitivity and 69% specificity to detect VSP<sup>[82]</sup>. Therefore, caution should be used to make therapeutic decisions based only on the absence of VSP of ACA or PCA by TCD. So, an increased mean CBFV on TCD is highly predictive of VSP of main intracranial arteries after aSAH. It is of critical importance to evaluate day-to-day changes in CBFV: Mean CBFV raising of 50 cm/s or more within 24-h<sup>[83]</sup> or mean CBFV increases of > 65 cm/s per day from day 3 to 7<sup>[11]</sup> indicates high risk for DCI (delayed cerebral ischaemia DCI), which is related to adverse outcome.

In conclusion, the association of clinical examination and different imaging techniques such as computed tomography and TCD should be used for diagnosis of VSP after aSAH instead of the single independent tests<sup>[84]</sup>.

The American Heart Association states that TCD could be considered a valid diagnostic tool to identify and to monitor the development of vasospasm on the management of aSAH<sup>[85]</sup>.

## TCD STUDY OF CEREBRAL AUTOREGULATION: IT'S APPLICATION IN ASAH, CAROTID DISEASE, AND SYNCOPE

Cerebral autoregulatory mechanism is a homeostatic function of local brain circulation which keeps CBF constant throughout a wide range of Cerebral Perfusion Pressure (estimated between 50 to 150 mmHg)<sup>[28]</sup>. Dysfunction of cerebrovascular autoregulation was shown in TBI<sup>[86]</sup>, ischemic cerebrovascular accidents<sup>[87]</sup>, carotid atherosclerosis<sup>[88]</sup>, and in syncope, although for the latter there is still uncertainty about its pathophysiological role<sup>[89]</sup>. Evaluation of cerebrovascular autoregulation can give useful prognostic information in these conditions<sup>[90]</sup>. The first evidences regarding physiologic cerebral circulatory autoregulation came from works which adopted a static approach measuring CBF after a pharmacologic modification of<sup>[90]</sup>. Following the introduction of TCD, CBFV could be used as an estimate of CBF, allowing dynamic monitoring of local cerebral blood flow.

TCD performed simultaneously with thigh cuff deflation was used for the first times by Aaslid<sup>[91]</sup> in 1989, after this many different nonpharmacologic stimuli were adopted in order to provoke a pressure modification, like pressure over carotid artery<sup>[92]</sup>, Valsalva manoeuvre<sup>[93]</sup>, head-up tilting<sup>[94]</sup>, and application of negative pressure to lower portion of the body<sup>[89,95]</sup>. In particular the static autoregulatory index (sARI), which is calculated as the percent of change in cerebrovascular resistance (CVR) divided by the percent of change in cerebral perfusional pressure (CPP).

$$\text{sARI}^{[96]} = \% \text{ change in CVR} / \% \text{ change in CPP}$$

This index is used to classify autoregulatory function



going from 0 (no response) to 1 (full response). Anyway it should be kept in mind that static methods need pharmacologic or mechanical stimulations which may not be allowed in critically ill patients<sup>[87,90,97]</sup>. Regarding dynamic study a cerebral autoregulatory function, there is no index which can be considered as gold standard<sup>[98]</sup>. The Mx index expresses the relationship among CPP and m CBF-V: A positivity of this index means that cerebro-vascular flow is pressure-dependent and absent autoragulation, a negative correlation is found when autoregulatory function is preserved<sup>[97,99]</sup>.

Tiecks *et al.*<sup>[96]</sup> introduced the dynamic autoregulatory index (dARI), a parameter which is obtained constructing, through graphic representations, a CBFV response curve following pressure modification and adapting it to 10 of hypothetical models CBFV, ranging from curve 0 (no autoregulatory function) to curve 9 (fully unaffected autoregulation)<sup>[96]</sup>.

In subjects affected by ICA stenosis, derangement of autoregulatory function can represent a marker of high risk of stroke and so it can be used to guide treatment decision making towards revascularization<sup>[88,100]</sup>. In fact significant decrease in dARI and increase in Mx indexes have been reported in patients with ipsilateral stenosis-occlusion of ICA, with a significant correlation with the severity of stenotic lesions<sup>[88,101]</sup>. On the other hand altered dARI and Mx indexes were only found in subjects with severely (> 80%-90%) stenotic carotid arteries and Mx index wasn't significantly different in symptomatic confronted with asymptomatic subjects<sup>[88,101]</sup>.

In the setting of severe SAH, Lang *et al.*<sup>[100]</sup> studied cerebral autoregulation through continuous monitoring of BP and CBFV recording in 12 patients, confronted with 40 controls. Autoregulatory function was impaired when compared with control subjects ( $P < 0.01$  for days 106, and  $P < 0.001$  for days 7013). They suggested that TCD could evaluate the entity of autoregulatory dysfunction in patients SAH and a derangement of autoregulation foretells VSP. Moreover the presence of VSP was associated with worsening of autoregulatory response and the degree of cerebral autoregulatory dysfunction in the first days after the event (days 1-6) has a negative prognostic value.

In stroke patients TCD showed a consistent ipsilateral cerebral autoregulation dysfunction, which was associated with the need of surgical decompression, the severity of neurological damage and poor outcome<sup>[101]</sup>. Many methodological issues of TCD, limit the application of this technique in clinical practice for the evaluation of cerebrovascular autoregulation.

The presence of many different static and dynamic stimuli used in many different studies of this subject, without a reference gold standard methodology to confront with and the absence of a single reference value to define an impairment autoregulatory function impede the comparison and synthesis of different study results<sup>[87,89,102]</sup>. Moreover many published works have been conducted with small samples and are statistically underpowered<sup>[89]</sup>.

In addition since the majority of TCD studies is focused on MCA, alterations of autoregulatory function of posterior cerebral vasculature or in regional cortical vessels may be overlooked<sup>[87]</sup>.

In conclusion, TCD imaging represents a promising technique for the study of cerebral autoregulatory function, thanks to its good temporal resolution, non invasive approach, and good cost-benefit ratio.

## TCD IN ACUTE ISCHAEMIC STROKE: DIAGNOSIS AND PROGNOSIS

The American Academy of Neurology Report of the Therapeutics and Technology Assessment Subcommittee states that TCD can accurately identify acute MCA occlusions with a sensitivity, specificity, PPV and NPV higher than 90%<sup>[29]</sup>, while for occlusion of ICA siphon, Vertebral Artery (VA) and BA shows 70% to 90% sensitivity and PPV and very high specificity and NPV<sup>[29]</sup>.

In the setting of acute stroke TCD has been confronted with magnetic resonance angiography (MRA) and CTA<sup>[103-105]</sup>: It has been especially used to assess steno-occlusive pathology of intracranial vessels, such as the terminal ICA, ICA siphon, and MCA. TCD is 100% specific and 93% sensitive for identification of MCA lesions, while MRA had a sensitivity of 46% and a specificity of 74% in the assessment of intracranial arteries. In the emergency department in patients with suspected acute cerebral ischemia, bedside TCD can give real-time information about cerebral blood flow adjunctive to that obtained by CTA<sup>[105]</sup>.

In ischemic stroke, TCD evidence of complete intracranial arterial occlusions predicted worse neurologic outcome, disability, or death after 90 d in 2 studies<sup>[106,107]</sup>. Normal TCD findings instead predicted early neurological improvement<sup>[29,108]</sup>.

Performing a TCD examination in the first 24 h of stroke symptom onset greatly increases the accuracy of early stroke subtype diagnosis (hemorrhagic vs ischemic). Moreover early and accurate detection of arterial occlusion guides emergency management in patients with acute ischemic cerebrovascular accident. It is universally recognized that clinical course of stroke may present either spontaneous improvements or worsening in relation to dynamic changes in cerebral blood flow. Thus the detection of such haemodynamic changes with the use of TCD may have an important prognostic role.

Cerebral blood flow before and after the administration of thrombolytic agents in ischemic cerebrovascular accident, is described by the thrombolysis in brain ischaemia (TIBI) score<sup>[108]</sup>. Post-thrombolysis flow is classified ranging from 0: Absent flow to 5: Normal flow<sup>[109]</sup>.

TIBI grade and its increase post-thrombolysis correlate with severity, survival, and clinical recovery in ischemic stroke<sup>[11,109-112]</sup>. As shown by a meta-analysis, reopening of the occluded vessel within a time window of 6 h from stroke symptoms onset, assessed by TCD imaging, portends a better clinical outcome at 48 h (OR

= 4.31, 95%CI: 2.67-6.97) and better functional status at 3 mo (OR = 6.75, 95%CI: 3.47-13.12)<sup>[113]</sup>.

Moreover a sudden improvement of TIBI score or its gradual improvement over 30 min denotes more effective vessel recanalization and has been correlated to a better early outcome, whereas those in whom flow restoration takes place after more than 30 min show a significantly worse clinical outcome<sup>[111]</sup>.

Furthermore, applying TIBI score to TCD, early re-occlusion (flow decrease  $\geq 1$  TIBI grade, within 2 h) after thrombolysis can be recognized. It has been found in about 34% of cases of initial reperfusion<sup>[112]</sup> and has been associated with a worse outcome at 3 mo and a reduction of survival when confronted with patients experiencing stable reperfusion of occluded artery<sup>[112]</sup>.

So, daily TCD examinations can be useful to recognize dynamic changes in cerebral circulation more time-effectively than a single neuroradiological study. Serial evaluation of cerebral hemodynamics in patients with acute cerebral ischemia improves the diagnostic accuracy and gives valuable information about monitoring and decision making.

In conclusion, TCD represents a low-cost and readily repeatable diagnostic imaging test characterized by sensitivity and specificity > 80% for ICA and MCA occlusion<sup>[99,101]</sup>.

It also gives useful information about prognosis in MCA occlusion<sup>[99,103,104]</sup>. However, CTA and MRA should still be used as first-line imaging tests in ischaemic stroke because TCD is operator dependent and has low diagnostic accuracy for posterior circulation occlusive pathology<sup>[114]</sup>.

### Sickle cell disease and ischemic stroke

Subjects affected by sickle cell anemia carry a high risk for brain cerebrovascular injuries including stroke and subclinical infarction and haemorrhagic accidents. The rate of ischemic cerebrovascular accidents in this setting is 600 for 100000 patient years<sup>[115]</sup>.

More frequently involved intracranial arteries are ICA, proximal MCA and ACA, adhesion of sickle cells to the vascular endothelium of these vessels results in progressive stenotic or occlusive phenomena.

Asymptomatic children with CBFV > 200 cm/s show an higher rate of stroke events reported as 10000 per 100000 patient-years<sup>[116]</sup>. Blood transfusions can effectively lower the rate of stroke by > 90%<sup>[117]</sup>. So for children between 2- and 6-year-old affected by sickle cell anaemia it is recommended to perform a screening by TCD on semestral or annual basis.

On TCD screening peak mean CBFV among major intracranial vessels is measured<sup>[118]</sup>. Subjects showing a peak time averaged CBFV in all the above mentioned vessels lower than 170 cm/s are considered at low risk<sup>[118]</sup>. Whereas a CBFV higher than 200 cm/s in any artery demands blood transfusion aiming to obtain a rate of pathologic haemoglobin lower than 30% in order to decrease the risk of stroke<sup>[118]</sup>.

The Stroke Prevention Trial in Sickle Cell Anemia

(STOP Trial) showed that chronic red-cell transfusion reduced the risk of a first stroke by 90% and TCD can be used to screen and identify children at greatest risk of cerebrovascular disease.

## TBI AND BRAIN STEM DEATH

Trauma represents, among neurological conditions, the principal cause of morbidity and mortality in people under 45 years of age<sup>[119]</sup>. It is characterized by thruphasic pattern in cerebral blood flow: Hypoperfusion at time 0, hyperperfusion between 24 to 72 h, vasospasm from days 4 to days 15, and finally by raised ICP<sup>[119,120]</sup>.

Final outcome of patients depends on two main causes: (1) the initial traumatic injury, which takes place at time of accident; and (2) the secondary consecutive pathogenic responses which represents consecutive pathologic processes starting at the moment of trauma and leads to late clinical manifestations (e.g., DCI due to VSP and intracranial hypertension are the most important secondary injuring factors).

TCD allows non invasive and repeatable bedside assessment of post-traumatic cerebrovascular hemodynamic alterations, providing useful prognostic information and has relevant implications for management of TBI patients<sup>[8,29]</sup>.

Moreover TCD in this setting may be useful as a non-invasive mean of calculating of CPP. Czosnyka *et al.*<sup>[102]</sup> studied the reliability of CPP using TCD-measured CBFV in MCA (mean and diastolic) in 96 patients with TBI (Glasgow Coma Scale < 13). The CPP measured by TCD and the calculated CPP (MAP minus ICP, measured using an intraparenchymal sensor) were compared. The results showed that in 71% of the studies, the estimation error was less than 10 mmHg and in 84% of the examinations, the error was less than 15 mmHg. The TCD method had a high positive predictive power (94%) for detecting low CPP (< 60 mmHg).

Although TCD study allows non-invasive estimation of ICP and CPP, and is widely considered a valuable alternative to invasive monitoring<sup>[2]</sup>, too many formulae have been proposed for this application, often carrying too wide confidence intervals and in many cases without full validation<sup>[2,8]</sup>. Thus TCD is more properly used to monitor dynamic changes in CPP instead of its real value in the setting of TBI<sup>[2]</sup>.

Cerebral hypoperfusion is correlated with outcome at 6 mo after TBI, so non invasive measurement of CBF through TCD has proven to give information about prognosis similar to invasive CBF assessment<sup>[121]</sup>.

During the 72 h post TBI, a reduced cerebral blood flow state, characterized by an MCA mean-CBFV lower than 35 cm/s has been associated with unfavourable outcome at 6 mo evaluated by Glasgow Outcome Score.

In addition, a worse outcome at 6 mo (GOS 1-3) was demonstrated in 50 patients with head injury in which TCD monitoring showed vasospasm and hyperaemia identified by interrogation of the MCA, ACA, and BA within 7 d from traumatic brain event, respect to the

absence of alterations in blood flow velocity<sup>[122]</sup>.

Peak mean-CBFV was also an independent predictor of outcome with higher CBFV values carrying an increased risk for worse outcome evaluated by Glasgow Outcome Score<sup>[123]</sup>.

Diagnosis of brain stem death is usually derived from physical examination and prolonged monitoring<sup>[124]</sup>. It can be confirmed with the use of ancillary diagnostic modalities, such as EEG, radionuclide scans, and angiography. TCD ultrasonography can be also used to support diagnosis of brain death. In addition it may be of great value in this indication, as it is portable, less time consuming, and can be performed at bedside. Arrest in cerebral circulation is a condition before the terminal state of brain stem death, and it can be evidenced by TCD if one of specific Doppler spectra listed below is obtained insonating BA and ICA or MCA of both sides in two different studies performed at least 30 min apart<sup>[125]</sup>:

- (1) an oscillating waveshape (equal systolic antegrade flow and diastolic retrograde flow, *i.e.*, zero net flow);
- (2) small systolic spikes of lasting less than 200 ms and with a PSV of less than 50 cm/s with no diastolic flow; or
- (3) The absence of intracranial flow not with concomitant specific findings in extracranial arteries. These peculiar findings come after the progressive increase in ICP which occurs after necrosis of a critically large amount of cerebral tissue.

In detail, when ICP reaches the level of diastolic arterial pressure, then cerebral perfusion will happen exclusively during systole, while with the increase of ICP at the level of systolic arterial pressure there will be no net cerebral blood flow. In this phase TCD will show an oscillatory Doppler signal, as mentioned above, with equalization of area under the envelope of forward and backward Doppler spectra, so that resulting net flow is zero: This pattern has been correlated with angiographic evidence of brain circulatory arrest. Fourteen Later ICP will continue to rise above the level of systolic arterial pressure, at this stage only systolic spikes can be recorded on Doppler spectrum and absence of diastolic flow.

Successively the amplitude of systolic those Doppler signals will progressively decrease, so that in the final stage blood flow will be completely abolished and no Doppler signal can be recorded. In this case the diagnosis of brain death needs to be confirmed by Doppler exploration of extracranial arteries (Common Carotid, ICA and VA). Compared with arteriography as gold standard TCD showed a 100% agreement for diagnosis of brain stem death<sup>[126]</sup>. A meta-analysis performed by the American Academy of Neurology have demonstrated for this technique a sensitivity of 89%-100% and a specificity of 97%-100%<sup>[29,127]</sup>.

The consensus document of Neurosonology Research Group of the World Federation of Neurology on diagnosis of cerebral circulatory arrest using Doppler-sonography confirms that extracranial and intracranial Doppler sonography is useful as a confirmatory test to establish irreversibility of cerebral circulatory arrest. Although optional, TCD is of special value when the therapeutic

use of sedative drugs renders EEG unreliable<sup>[128]</sup>. This statement also mentions that the absence of flow in MCA precedes complete loss of brain stem functions. The AAN considers TCD a confirmatory test of brain death along with clinical testing and other allied tests<sup>[129]</sup>.

## CONCLUSION

To conclude, in NCCU TCD examination should be routinely recommended as a non invasive tool, which allows early identification of patients progressing to VSP secondary to aSAH and TBI. Moreover TCD can be used in NCCU for bed side assessment of CPP with acceptable reliability. The frequency with which TCD should be performed may be guided by patient clinical presentation, risk factors for VSP, and early clinical course. The presence and temporal profile of CBFVs in all available vessels must be detected and serially monitored. The high sensitivity of TCD to identify abnormally high CBFVs due to the onset of VSP demonstrates that TCD is an excellent first-line examination to identify those patients who may need urgent aggressive treatment. Several features of TCD assessment of VSP are similar to cerebral angiography. Most likely, validation of new TCD criteria for VSP and combination of different physiologic monitoring modalities that includes TCD, electroencephalography, brain tissue oxygen monitoring, cerebral microdialysis, and near-infrared spectroscopy will improve TCD accuracy to predict clinical deterioration and infarction from DCI.

## REFERENCES

- 1 **Aaslid R**, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg* 1982; **57**: 769-774 [PMID: 7143059 DOI: 10.3171/jns.1982.57.6.0769]
- 2 **Saqqur M**, Zygun D, Demchuk A. Role of transcranial Doppler in neurocritical care. *Crit Care Med* 2007; **35**: S216-S223 [PMID: 17446782 DOI: 10.1097/01.CCM.0000260633.66384.FB]
- 3 **Di Tullio M**, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med* 1992; **117**: 461-465 [PMID: 1503349 DOI: 10.7326/0003-4819-117-6-461]
- 4 **Ghosh S**, Ghosh AK, Ghosh SK. Patent foramen ovale and atrial septal aneurysm in cryptogenic stroke. *Postgrad Med J* 2007; **83**: 173-177 [PMID: 17344571 DOI: 10.1136/pgmj.2006.051094]
- 5 **Arenillas JF**, Molina CA, Montaner J, Abilleira S, González-Sánchez MA, Alvarez-Sabín J. Progression and clinical recurrence of symptomatic middle cerebral artery stenosis: a long-term follow-up transcranial Doppler ultrasound study. *Stroke* 2001; **32**: 2898-2904 [PMID: 11739993 DOI: 10.1161/hs1201.099652]
- 6 **Christou I**, Felberg RA, Demchuk AM, Grotta JC, Burgin WS, Malkoff M, Alexandrov AV. A broad diagnostic battery for bedside transcranial Doppler to detect flow changes with internal carotid artery stenosis or occlusion. *J Neuroimaging* 2001; **11**: 236-242 [PMID: 11462288 DOI: 10.1111/j.1552-6569.2001.tb00040.x]
- 7 **Rigamonti A**, Ackery A, Baker AJ. Transcranial Doppler monitoring in subarachnoid hemorrhage: a critical tool in critical care. *Can J Anaesth* 2008; **55**: 112-123 [PMID: 18245071 DOI: 10.1007/BF03016323]
- 8 **White H**, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. *Intensive Care Med* 2006; **32**: 981-994 [PMID: 16791661 DOI: 10.1007/s00134-006-0173-y]
- 9 **Bogdahn U**, Becker G, Winkler J, Greiner K, Perez J, Meurers B.



- Transcranial color-coded real-time sonography in adults. *Stroke* 1990; **21**: 1680-1688 [PMID: 2264074 DOI: 10.1161/01.STR.21.12.1680]
- 10 **Antignani PL**, Benedetti-Valentini F, Aluigi L, Baroncelli TA, Camporese G, Failla G, Martinelli O, Palasciano GC, Pulli R, Rispoli P, Amato A, Amitrano M, Dorigo W, Gossetti B, Itrace L, Laurito A, Magnoni F, Minucci S, Pedrini L, Righi D, Verlatto F. Diagnosis of vascular diseases. Ultrasound investigations--guidelines. *Int Angiol* 2012; **31**: 1-77 [PMID: 23470846]
  - 11 **Tsivgoulis G**, Alexandrov AV, Sloan MA. Advances in transcranial Doppler ultrasonography. *Curr Neurol Neurosci Rep* 2009; **9**: 46-54 [PMID: 19080753 DOI: 10.1007/s11910-009-0008-7]
  - 12 **Marinoni M**, Ginanneschi A, Forleo P, Amaducci L. Technical limits in transcranial Doppler recording: inadequate acoustic windows. *Ultrasound Med Biol* 1997; **23**: 1275-1277 [PMID: 9372576 DOI: 10.1016/S0301-5629(97)00077-X]
  - 13 **Babikian V**, Sloan MA, Tegeler CH, DeWitt LD, Fayad PB, Feldmann E, Gomez CR. Transcranial Doppler validation pilot study. *J Neuroimaging* 1993; **3**: 242-249 [PMID: 10150152 DOI: 10.1111/jon199334242]
  - 14 **Bouzat P**, Oddo M, Payen JF. Transcranial Doppler after traumatic brain injury: is there a role? *Curr Opin Crit Care* 2014; **20**: 153-160 [PMID: 24531654 DOI: 10.1097/MCC.0000000000000071]
  - 15 **Paulus J**, Cinotti R, Hamel O, Buffenoir K, Asehnoune K. The echographic "butterfly wing" aspect of the sphenoid bone is a critical landmark to insulate the middle cerebral artery. *Intensive Care Med* 2014; **40**: 1783-1784 [PMID: 25164395 DOI: 10.1007/s00134-014-3447-9]
  - 16 **Aaslid R**, Huber P, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. *J Neurosurg* 1984; **60**: 37-41 [PMID: 6689726 DOI: 10.3171/jns.1984.60.1.0037]
  - 17 **Aaslid R**. The Doppler principle applied to measurement of blood flow velocity in cerebral arteries. in Vienna RA Transcranial Doppler Sonography, New York, Springer, 1986: 22-38 [DOI: 10.1007/978-3-7091-8864-4\_3]
  - 18 **Tegeler CH**, Crutchfield K, Katsnelson M, Kim J, Tang R, Passmore Griffin L, Rundek T, Evans G. Transcranial Doppler velocities in a large, healthy population. *J Neuroimaging* 2013; **23**: 466-472 [PMID: 23157483 DOI: 10.1111/j.1552-6569.2012.00711.x]
  - 19 **Nicoletto HA**, Burkman MH. Transcranial Doppler series part II: performing a transcranial Doppler. *Am J Electroneurodiagnostic Technol* 2009; **49**: 14-27 [PMID: 19388548]
  - 20 **Arnolds BJ**, von Reutern GM. Transcranial Doppler sonography. Examination technique and normal reference values. *Ultrasound Med Biol* 1986; **12**: 115-123 [PMID: 2943067 DOI: 10.1016/0301-5629(86)90016-5]
  - 21 **Moppett IK**, Mahajan RP. Transcranial Doppler ultrasonography in anaesthesia and intensive care. *Br J Anaesth* 2004; **93**: 710-724 [PMID: 15220174 DOI: 10.1093/bja/ae205]
  - 22 **Droste DW**, Harders AG, Rastogi E. A transcranial Doppler study of blood flow velocity in the middle cerebral arteries performed at rest and during mental activities. *Stroke* 1989; **20**: 1005-1011 [PMID: 2667197 DOI: 10.1161/01.STR.20.8.1005]
  - 23 **Patel PM**, Drummond JC. Cerebral physiology and the effects of anesthetic drugs. In Miller's Anesthesia 7th edition. New York: Churchill Livingstone, 2009: 305-340
  - 24 **Shahlaie K**, Keachie K, Hutchins IM, Rudisill N, Madden LK, Smith KA, Ko KA, Latchaw RE, Muizelaar JP. Risk factors for posttraumatic vasospasm. *J Neurosurg* 2011; **115**: 602-611 [PMID: 21663415 DOI: 10.3171/2011.5.JNS101667]
  - 25 **Kaps M**, Stolz E, Allendoerfer J. Prognostic value of transcranial sonography in acute stroke patients. *Eur Neurol* 2008; **59** Suppl 1: 9-16 [PMID: 18382108 DOI: 10.1159/000114455]
  - 26 **Lindgaard KF**, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. Cerebral vasospasm after subarachnoid haemorrhage investigated by means of transcranial Doppler ultrasound. *Acta Neurochir Suppl (Wien)* 1988; **42**: 81-84 [PMID: 3055838 DOI: 10.1007/978-3-7091-8975-7\_16]
  - 27 **Martin PJ**, Evans DH, Naylor AR. Transcranial color-coded sonography of the basal cerebral circulation. Reference data from 115 volunteers. *Stroke* 1994; **25**: 390-396 [PMID: 7905680 DOI: 10.1161/01.STR.25.2.390]
  - 28 **Rasulo FA**, De Peri E, Lavinio A. Transcranial Doppler ultrasonography in intensive care. *Eur J Anaesthesiol Suppl* 2008; **42**: 167-173 [PMID: 18289437 DOI: 10.1017/S0265021507003341]
  - 29 **Sloan MA**, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, Wechsler LR, Newell DW, Gomez CR, Babikian VL, Lefkowitz D, Goldman RS, Armon C, Hsu CY, Goodin DS. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2004; **62**: 1468-1481 [PMID: 15136667 DOI: 10.1212/WNL.62.9.1468]
  - 30 **Cabanes L**, Mas JL, Cohen A, Amarencio P, Cabanes PA, Oubary P, Chedru F, Guérin F, Bousser MG, de Recondo J. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke* 1993; **24**: 1865-1873 [PMID: 8248969 DOI: 10.1161/01.STR.24.12.1865]
  - 31 **D'Andrea A**, Calabrò R. The diagnosis of cryptogenic stroke: is the combined ultrasound approach the right choice? *J Cardiovasc Med (Hagerstown)* 2011; **12**: 527-529 [PMID: 21720222 DOI: 10.2459/JCM.0b013e32834976d6]
  - 32 **Sarkar S**, Ghosh S, Ghosh SK, Collier A. Role of transcranial Doppler ultrasonography in stroke. *Postgrad Med J* 2007; **83**: 683-689 [PMID: 17989267 DOI: 10.1136/pgmj.2007.058602]
  - 33 **Kerut EK**, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol* 2001; **38**: 613-623 [PMID: 11527606 DOI: 10.1016/S0735-1097(01)01427-9]
  - 34 **Hara H**, Virmani R, Ladich E, Mackey-Bojack S, Titus J, Reisman M, Gray W, Nakamura M, Mooney M, Poulouse A, Schwartz RS. Patent foramen ovale: current pathology, pathophysiology, and clinical status. *J Am Coll Cardiol* 2005; **46**: 1768-1776 [PMID: 16256883 DOI: 10.1016/j.jacc.2005.08.038]
  - 35 **Wu LA**, Malouf JF, Dearani JA, Hagler DJ, Reeder GS, Petty GW, Khandheria BK. Patent foramen ovale in cryptogenic stroke: current understanding and management options. *Arch Intern Med* 2004; **164**: 950-956 [PMID: 15136302 DOI: 10.1001/archinte.164.9.950]
  - 36 **Hagen PT**, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984; **59**: 17-20 [PMID: 6694427]
  - 37 **Knauth M**, Ries S, Pohmann S, Kerby T, Forsting M, Daffertshofer M, Hennerici M, Sartor K. Cohort study of multiple brain lesions in sport divers: role of a patent foramen ovale. *BMJ* 1997; **314**: 701-705 [PMID: 9116544 DOI: 10.1136/bmj.314.7082.701]
  - 38 **Godart F**, Rey C, Prat A, Vincentelli A, Chmait A, Francart C, Porte H. Atrial right-to-left shunting causing severe hypoxaemia despite normal right-sided pressures. Report of 11 consecutive cases corrected by percutaneous closure. *Eur Heart J* 2000; **21**: 483-489 [PMID: 10681489 DOI: 10.1053/euhj.1999.1944]
  - 39 **Lamy C**, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, Coste J, Mas JL. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. *Stroke* 2002; **33**: 706-711 [PMID: 11872892 DOI: 10.1161/hs0302.104543]
  - 40 **Homma S**, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002; **105**: 2625-2631 [PMID: 12045168 DOI: 10.1161/01.CIR.0000017498.88393.44]
  - 41 **Woods TD**, Patel A. A critical review of patent foramen ovale detection using saline contrast echocardiography: when bubbles lie. *J Am Soc Echocardiogr* 2006; **19**: 215-222 [PMID: 16455428 DOI: 10.1016/j.echo.2005.09.023]
  - 42 **Meltzer RS**, Tickner EG, Sahines TP, Popp RL. The source of ultrasound contrast effect. *J Clin Ultrasound* 1980; **8**: 121-127 [PMID: 6767744 DOI: 10.1002/jcu.1870080205]
  - 43 **Lefèvre J**, Lafitte S, Reant P, Perron JM, Roudaut R. Optimization of patent foramen ovale detection by contrast transthoracic echo-

- cardiography using second harmonic imaging. *Arch Cardiovasc Dis* 2008; **101**: 213-219 [PMID: 18654095 DOI: 10.1016/S1875-2136(08)73695-7]
- 44 **Van Camp G**, Franken P, Melis P, Cosyns B, Schoors D, Vanoerschelde JL. Comparison of transthoracic echocardiography with second harmonic imaging with transesophageal echocardiography in the detection of right to left shunts. *Am J Cardiol* 2000; **86**: 1284-1287, A9 [PMID: 11090813 DOI: 10.1016/S0002-9149(00)01224-8]
  - 45 **Kühl HP**, Hoffmann R, Merx MW, Franke A, Klötzsch C, Lepper W, Reineke T, Noth J, Hanrath P. Transthoracic echocardiography using second harmonic imaging: diagnostic alternative to transesophageal echocardiography for the detection of atrial right to left shunt in patients with cerebral embolic events. *J Am Coll Cardiol* 1999; **34**: 1823-1830 [PMID: 10577576 DOI: 10.1016/S0735-1097(99)00412-X]
  - 46 **Jauss M**, Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. *Cerebrovasc Dis* 2000; **10**: 490-496 [PMID: 11070388 DOI: 10.1159/000016119]
  - 47 **Rajamani K**, Gorman M. Transcranial Doppler in stroke. *Biomed Pharmacother* 2001; **55**: 247-257 [PMID: 11428550 DOI: 10.1016/S0753-3322(01)00063-4]
  - 48 **Serena J**, Segura T, Perez-Ayuso MJ, Bassaganyas J, Molins A, Dávalos A. The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. *Stroke* 1998; **29**: 1322-1328 [PMID: 9660381 DOI: 10.1161/01.STR.29.7.1322]
  - 49 **Lange MC**, Zétola VF, deSouza AM, Novak FM, Piovesan EJ, Werneck LC. Intracranial embolism characteristics in PFO patients: a comparison between positive and negative PFO by transesophageal echocardiography: the rule of nine. *J Neurol Sci* 2010; **293**: 106-109 [PMID: 20363000 DOI: 10.1016/j.jns.2010.02.003]
  - 50 **Meier B**, Lock JE. Contemporary management of patent foramen ovale. *Circulation* 2003; **107**: 5-9 [PMID: 12515733 DOI: 10.1161/01.CIR.0000046073.34261.C1]
  - 51 **Mojadidi MK**, Roberts SC, Winoker JS, Romero J, Goodman-Meza D, Gevorgyan R, Tobis JM. Accuracy of transcranial Doppler for the diagnosis of intracardiac right-to-left shunt: a bivariate meta-analysis of prospective studies. *JACC Cardiovasc Imaging* 2014; **7**: 236-250 [PMID: 24560213 DOI: 10.1016/j.jcmg.2013.12.011]
  - 52 **González-Alujas T**, Evangelista A, Santamarina E, Rubiera M, Gómez-Bosch Z, Rodríguez-Palomares JF, Avegliano G, Molina C, Alvarez-Sabín J, García-Dorado D. Diagnosis and quantification of patent foramen ovale. Which is the reference technique? Simultaneous study with transcranial Doppler, transthoracic and transesophageal echocardiography. *Rev Esp Cardiol* 2011; **64**: 133-139 [PMID: 21277667 DOI: 10.1016/j.recesp.2010.10.009]
  - 53 **Zoghbi WA**. Patent foramen ovale: going beyond the bubbles. *JACC Cardiovasc Imaging* 2014; **7**: 251-253 [PMID: 24651099 DOI: 10.1016/j.jcmg.2014.01.007]
  - 54 **Johansson MC**, Eriksson P, Guron CW, Dellborg M. Pitfalls in diagnosing PFO: characteristics of false-negative contrast injections during transesophageal echocardiography in patients with patent foramen ovals. *J Am Soc Echocardiogr* 2010; **23**: 1136-1142 [PMID: 20850947 DOI: 10.1016/j.echo.2010.08.004]
  - 55 **Souteyrand G**, Motreff P, Lussan JR, Rodriguez R, Geoffroy E, Dauphin C, Boire JY, Lamaison D, Cassagnes J. Comparison of transthoracic echocardiography using second harmonic imaging, transcranial Doppler and transesophageal echocardiography for the detection of patent foramen ovale in stroke patients. *Eur J Echocardiogr* 2006; **7**: 147-154 [PMID: 15927538 DOI: 10.1016/j.euje.2005.04.007]
  - 56 **Clarke NR**, Timperley J, Kelion AD, Banning AP. Transthoracic echocardiography using second harmonic imaging with Valsalva manoeuvre for the detection of right to left shunts. *Eur J Echocardiogr* 2004; **5**: 176-181 [PMID: 15147659 DOI: 10.1016/S1525-2167(03)00076-3]
  - 57 **Daniëls C**, Weytjens C, Cosyns B, Schoors D, De Sutter J, Paelinck B, Muyldermans L, Van Camp G. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. *Eur J Echocardiogr* 2004; **5**: 449-452 [PMID: 15556821 DOI: 10.1016/j.euje.2004.04.004]
  - 58 **Inzitari D**. The Italian Guidelines for stroke prevention. The Stroke Prevention and Educational Awareness Diffusion (SPREAD) Collaboration. *Neurol Sci* 2000; **21**: 5-12 [PMID: 10938196 DOI: 10.1007/s100720070112]
  - 59 **Inzitari D**, Carlucci G. Italian Stroke Guidelines (SPREAD): evidence and clinical practice. *Neurol Sci* 2006; **27** Suppl 3: S225-S227 [PMID: 16752053 DOI: 10.1007/s10072-006-0622-y]
  - 60 **Pristipino C**, Anzola GP, Ballerini L, Bartorelli A, Cecconi M, Chessa M, Donti A, Gaspardone A, Neri G, Onorato E, Palareti G, Rakar S, Rigatelli G, Santoro G, Toni D, Ussia GP, Violini R, Guagliumi G, Bedogni F, Cremonesi A. [Multidisciplinary position paper on the management of patent foramen ovale in the presence of cryptogenic cerebral ischemia - Italian version 2013]. *G Ital Cardiol (Rome)* 2013; **14**: 699-712 [PMID: 24121896 DOI: 10.1714/1335.14838]
  - 61 **Anzola GP**, Morandi E, Casilli F, Onorato E. Does transcatheter closure of patent foramen ovale really "shut the door?" A prospective study with transcranial Doppler. *Stroke* 2004; **35**: 2140-2144 [PMID: 15284445 DOI: 10.1161/01.STR.0000137764.07815.de]
  - 62 **Sorensen SG**, Aguilar H, McKnight WK, Thomas H, Muhlestein JB. Transcranial Doppler quantification of residual shunt after percutaneous patent foramen ovale closure. Comparison of two devices. *J Interv Cardiol* 2010; **23**: 575-580 [PMID: 20796165 DOI: 10.1111/j.1540-8183.2010.00587.x]
  - 63 **Ursino M**, Giulioni M. Quantitative assessment of cerebral autoregulation from transcranial Doppler pulsatility: a computer simulation study. *Med Eng Phys* 2003; **25**: 655-666 [PMID: 12900181 DOI: 10.1016/S1350-4533(02)00251-5]
  - 64 **Chang JJ**, Tsvigoulis G, Katsanos AH, Malkoff MD, Alexandrov AV. Diagnostic Accuracy of Transcranial Doppler for Brain Death Confirmation: Systematic Review and Meta-Analysis. *AJNR Am J Neuroradiol* 2016; **37**: 408-414 [PMID: 26514611]
  - 65 **Moreno JA**, Mesalles E, Gener J, Tomasa A, Ley A, Roca J, Fernández-Llamazares J. Evaluating the outcome of severe head injury with transcranial Doppler ultrasonography. *Neurosurg Focus* 2000; **8**: e8 [PMID: 16906703 DOI: 10.3171/foc.2000.8.1.1702]
  - 66 **Velat GJ**, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: review of randomized controlled trials and meta-analyses in the literature. *World Neurosurg* 2011; **76**: 446-454 [PMID: 22152574 DOI: 10.1016/j.wneu.2011.02.030]
  - 67 **Dorsch N**. A clinical review of cerebral vasospasm and delayed ischaemia following aneurysm rupture. *Acta Neurochir Suppl* 2011; **110**: 5-6 [PMID: 21116906 DOI: 10.1007/978-3-7091-0353-1\_1]
  - 68 **Papaioannou V**, Dragoumanis C, Theodorou V, Konstantonis D, Pneumatikos I, Birbilis T. Transcranial Doppler ultrasonography in intensive care unit. Report of a case with subarachnoid hemorrhage and brain death and review of the literature. *Greek ej Periop Med* 2008; **6**: 95-104
  - 69 **Biller J**, Godersky JC, Adams HP. Management of aneurysmal subarachnoid hemorrhage. *Stroke* 1988; **19**: 1300-1305 [PMID: 3176090 DOI: 10.1161/01.STR.19.10.1300]
  - 70 **Harders AG**, Gilsbach JM. Time course of blood velocity changes related to vasospasm in the circle of Willis measured by transcranial Doppler ultrasound. *J Neurosurg* 1987; **66**: 718-728 [PMID: 3553456 DOI: 10.3171/jns.1987.66.5.0718]
  - 71 **Armonda RA**, Bell RS, Vo AH, Ling G, DeGraba TJ, Crandall B, Ecklund J, Campbell WW. Wartime traumatic cerebral vasospasm: recent review of combat casualties. *Neurosurgery* 2006; **59**: 1215-1225; discussion 1225 [PMID: 17277684 DOI: 10.1227/01.NEU.0000249190.46033.94]
  - 72 **Keyrouz SG**, Diringner MN. Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. *Crit Care* 2007; **11**: 220 [PMID: 17705883 DOI: 10.1186/cc5958]
  - 73 **Rowland MJ**, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. *Br J Anaesth* 2012; **109**: 315-329 [PMID: 22879655 DOI: 10.1093/bja/aes264]



- 74 **Topcuoglu MA**, Pryor JC, Ogilvy CS, Kistler JP. Cerebral Vasospasm Following Subarachnoid Hemorrhage. *Curr Treat Options Cardiovasc Med* 2002; **4**: 373-384 [PMID: 12194810 DOI: 10.1007/s11936-002-0017-1]
- 75 **Sviri GE**, Ghodke B, Britz GW, Douville CM, Haynor DR, Mesiwala AH, Lam AM, Newell DW. Transcranial Doppler grading criteria for basilar artery vasospasm. *Neurosurgery* 2006; **59**: 360-366; discussion 360-366 [PMID: 16883176 DOI: 10.1227/01.NEU.0000223502.93013.6E]
- 76 **Bederson JB**, Connolly ES, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE, Harbaugh RE, Patel AB, Rosenwasser RH. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 2009; **40**: 994-1025 [PMID: 19164800 DOI: 10.1161/STROKEAHA.108.191395]
- 77 **McGirt MJ**, Blessing RP, Goldstein LB. Transcranial Doppler monitoring and clinical decision-making after subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis* 2003; **12**: 88-92 [PMID: 17903910 DOI: 10.1053/jscd.2003.10]
- 78 **Washington CW**, Zipfel GJ. Detection and monitoring of vasospasm and delayed cerebral ischemia: a review and assessment of the literature. *Neurocrit Care* 2011; **15**: 312-317 [PMID: 21748499 DOI: 10.1007/s12028-011-9594-8]
- 79 **Lysakowski C**, Walder B, Costanza MC, Tramèr MR. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: A systematic review. *Stroke* 2001; **32**: 2292-2298 [PMID: 11588316 DOI: 10.1161/hs1001.097108]
- 80 **Harders A**, Gilsbach J. Transcranial Doppler sonography and its application in extracranial-intracranial bypass surgery. *Neurol Res* 1985; **7**: 129-141 [PMID: 2866457]
- 81 **Skjelland M**, Krohg-Sørensen K, Tennøe B, Bakke SJ, Brucher R, Russell D. Cerebral microemboli and brain injury during carotid artery endarterectomy and stenting. *Stroke* 2009; **40**: 230-234 [PMID: 18927460 DOI: 10.1161/STROKEAHA.107.513341]
- 82 **Wozniak MA**, Sloan MA, Rothman MI, Burch CM, Rigamonti D, Permutt T, Numaguchi Y. Detection of vasospasm by transcranial Doppler sonography. The challenges of the anterior and posterior cerebral arteries. *J Neuroimaging* 1996; **6**: 87-93 [PMID: 8634493 DOI: 10.1111/joni19966287]
- 83 **Frontera JA**, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, Connolly ES, Mayer SA. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? *Stroke* 2009; **40**: 1963-1968 [PMID: 19359629 DOI: 10.1161/STROKEAHA.108.544700]
- 84 **Gonzalez NR**, Boscardin WJ, Glenn T, Vinuela F, Martin NA. Vasospasm probability index: a combination of transcranial doppler velocities, cerebral blood flow, and clinical risk factors to predict cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2007; **107**: 1101-1112 [PMID: 18077946 DOI: 10.3171/JNS-07/12/1101]
- 85 **Connolly ES**, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; **43**: 1711-1737 [PMID: 22556195 DOI: 10.1161/STR.0b013e3182587839]
- 86 **Puppo C**, López L, Caragna E, Biestro A. One-minute dynamic cerebral autoregulation in severe head injury patients and its comparison with static autoregulation. A transcranial Doppler study. *Neurocrit Care* 2008; **8**: 344-352 [PMID: 18363042 DOI: 10.1007/s12028-008-9069-8]
- 87 **Aries MJ**, Elting JW, De Keyser J, Kremer BP, Vroomen PC. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke* 2010; **41**: 2697-2704 [PMID: 20930158 DOI: 10.1161/STROKEAHA.110.594168]
- 88 **Reinhard M**, Roth M, Müller T, Czosnyka M, Timmer J, Hetzel A. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. *Stroke* 2003; **34**: 2138-2144 [PMID: 12920261 DOI: 10.1161/01.STR.0000087788.65566.AC]
- 89 **Panerai RB**. Transcranial Doppler for evaluation of cerebral autoregulation. *Clin Auton Res* 2009; **19**: 197-211 [PMID: 19370374 DOI: 10.1007/s10286-009-0011-8]
- 90 **Panerai RB**. Assessment of cerebral pressure autoregulation in humans—a review of measurement methods. *Physiol Meas* 1998; **19**: 305-338 [PMID: 9735883 DOI: 10.1088/0967-3334/19/3/001]
- 91 **Aaslid R**, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989; **20**: 45-52 [PMID: 2492126 DOI: 10.1161/01.STR.20.1.45]
- 92 **Giller CA**. A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. *Acta Neurochir (Wien)* 1991; **108**: 7-14 [PMID: 2058430 DOI: 10.1007/BF01407660]
- 93 **Tiecks FP**, Douville C, Byrd S, Lam AM, Newell DW. Evaluation of impaired cerebral autoregulation by the Valsalva maneuver. *Stroke* 1996; **27**: 1177-1182 [PMID: 8685924 DOI: 10.1161/01.STR.27.7.1177]
- 94 **Schondorf R**, Stein R, Roberts R, Benoit J, Cupples W. Dynamic cerebral autoregulation is preserved in neurally mediated syncope. *J Appl Physiol* (1985) 2001; **91**: 2493-2502 [PMID: 11717210]
- 95 **Levine BD**, Giller CA, Lane LD, Buckley JC, Blomqvist CG. Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. *Circulation* 1994; **90**: 298-306 [PMID: 8026012 DOI: 10.1161/01.CIR.90.1.298]
- 96 **Tiecks FP**, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995; **26**: 1014-1019 [PMID: 7762016 DOI: 10.1161/01.STR.26.6.1014]
- 97 **Czosnyka M**, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. *Neurocrit Care* 2009; **10**: 373-386 [PMID: 19127448 DOI: 10.1007/s12028-008-9175-7]
- 98 **Panerai RB**. Cerebral autoregulation: from models to clinical applications. *Cardiovasc Eng* 2008; **8**: 42-59 [PMID: 18041584 DOI: 10.1007/s10558-007-9044-6]
- 99 **Czosnyka M**, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 1996; **27**: 1829-1834 [PMID: 8841340 DOI: 10.1161/01.STR.27.10.1829]
- 100 **Lang EW**, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. *Crit Care Med* 2001; **29**: 158-163 [PMID: 11176177 DOI: 10.1097/00003246-200101000-00031]
- 101 **White RP**, Markus HS. Impaired dynamic cerebral autoregulation in carotid artery stenosis. *Stroke* 1997; **28**: 1340-1344 [PMID: 9227680 DOI: 10.1161/01.STR.28.7.1340]
- 102 **Czosnyka M**, Matta BF, Smielewski P, Kirkpatrick PJ, Pickard JD. Cerebral perfusion pressure in head-injured patients: a noninvasive assessment using transcranial Doppler ultrasonography. *J Neurosurg* 1998; **88**: 802-808 [PMID: 9576246 DOI: 10.3171/jns.1998.88.5.802]
- 103 **Demchuk AM**, Christou I, Wein TH, Felberg RA, Malkoff M, Grotta JC, Alexandrov AV. Accuracy and criteria for localizing arterial occlusion with transcranial Doppler. *J Neuroimaging* 2000; **10**: 1-12 [PMID: 10666975 DOI: 10.1111/jon20001011]
- 104 **Razumovsky AY**, Gillard JH, Bryan RN, Hanley DF, Oppenheimer SM. TCD, MRA and MRI in acute cerebral ischemia. *Acta Neurol Scand* 1999; **99**: 65-76 [PMID: 9925241 DOI: 10.1111/j.1600-0404.1999.tb00660.x]
- 105 **Tsivgoulis G**, Sharma VK, Lao AY, Malkoff MD, Alexandrov AV. Validation of transcranial Doppler with computed tomography angiography in acute cerebral ischemia. *Stroke* 2007; **38**: 1245-1249 [PMID: 17332465 DOI: 10.1161/01.STR.0000259712.64772.85]
- 106 **Camerlingo M**, Casto L, Corsi B, Servalli MC, Ferraro B, Mamoli A. Prognostic use of ultrasonography in acute non-hemorrhagic carotid stroke. *Ital J Neurol Sci* 1996; **17**: 215-218 [PMID: 8856412 DOI: 10.1007/BF01995686]
- 107 **Baracchini C**, Manara R, Ermani M, Meneghetti G. The quest for early predictors of stroke evolution: can TCD be a guiding light?

- Stroke 2000; **31**: 2942-2947 [PMID: 11108753 DOI: 10.1161/01.STR.31.12.2942]
- 108 **Kushner MJ**, Zanette EM, Bastianello S, Mancini G, Sacchetti ML, Carolei A, Bozzao L. Transcranial Doppler in acute hemispheric brain infarction. *Neurology* 1991; **41**: 109-113 [PMID: 1985274 DOI: 10.1212/WNL.41.1.109]
- 109 **Demchuk AM**, Burgin WS, Christou I, Felberg RA, Barber PA, Hill MD, Alexandrov AV. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke* 2001; **32**: 89-93 [PMID: 11136920 DOI: 10.1161/01.STR.32.1.89]
- 110 **Christou I**, Alexandrov AV, Burgin WS, Wojner AW, Felberg RA, Malkoff M, Grotta JC. Timing of recanalization after tissue plasminogen activator therapy determined by transcranial doppler correlates with clinical recovery from ischemic stroke. *Stroke* 2000; **31**: 1812-1816 [PMID: 10926939]
- 111 **Alexandrov AV**, Burgin WS, Demchuk AM, El-Mitwalli A, Grotta JC. Speed of intracranial clot lysis with intravenous tissue plasminogen activator therapy: sonographic classification and short-term improvement. *Circulation* 2001; **103**: 2897-2902 [PMID: 11413077 DOI: 10.1161/01.CIR.103.24.2897]
- 112 **Alexandrov AV**, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. *Neurology* 2002; **59**: 862-867 [PMID: 12297567 DOI: 10.1212/WNL.59.6.862]
- 113 **Stolz E**, Cioli F, Allendoerfer J, Gerriets T, Del Sette M, Kaps M. Can early neurosonology predict outcome in acute stroke?: a metaanalysis of prognostic clinical effect sizes related to the vascular status. *Stroke* 2008; **39**: 3255-3261 [PMID: 18845799 DOI: 10.1161/STROKEAHA.108.522714]
- 114 **Jauch EC**, Saver JL, Adams HP, Bruno A, Connors JJ, Demerschalk BM, Khatri P, McMullan PW, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 870-947 [PMID: 23370205 DOI: 10.1161/STR.0b013e318284056a]
- 115 **Platt OS**. Prevention and management of stroke in sickle cell anemia. *Hematology Am Soc Hematol Educ Program* 2006; 54-57 [PMID: 17124040 DOI: 10.1182/asheducation-2006.1.54]
- 116 **Adams RJ**, McKie VC, Carl EM, Nichols FT, Perry R, Brock K, McKie K, Figueroa R, Litaker M, Weiner S, Brambilla D. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. *Ann Neurol* 1997; **42**: 699-704 [PMID: 9392568 DOI: 10.1002/ana.410420505]
- 117 **Adams RJ**, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998; **339**: 5-11 [PMID: 9647873 DOI: 10.1056/NEJM199807023390102]
- 118 **Adams RJ**. TCD in sickle cell disease: an important and useful test. *Pediatr Radiol* 2005; **35**: 229-234 [PMID: 15703904 DOI: 10.1007/s00247-005-1409-7]
- 119 **Werner C**, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth* 2007; **99**: 4-9 [PMID: 17573392 DOI: 10.1093/bja/aem131]
- 120 **Martin NA**, Patwardhan RV, Alexander MJ, Africk CZ, Lee JH, Shalmon E, Hovda DA, Becker DP. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. *J Neurosurg* 1997; **87**: 9-19 [PMID: 9202259 DOI: 10.3171/jns.1997.87.1.0009]
- 121 **Jaggi JL**, Obrist WD, Gennarelli TA, Langfitt TW. Relationship of early cerebral blood flow and metabolism to outcome in acute head injury. *J Neurosurg* 1990; **72**: 176-182 [PMID: 2295915 DOI: 10.3171/jns.1990.72.2.0176]
- 122 **van Santbrink H**, Schouten JW, Steyerberg EW, Avezaat CJ, Maas AI. Serial transcranial Doppler measurements in traumatic brain injury with special focus on the early posttraumatic period. *Acta Neurochir (Wien)* 2002; **144**: 1141-1149 [PMID: 12434170 DOI: 10.1007/s00701-002-1012-8]
- 123 **Zuryski YA**, Dorsch NW, Fearnside MR. Incidence and effects of increased cerebral blood flow velocity after severe head injury: a transcranial Doppler ultrasound study II. Effect of vasospasm and hyperemia on outcome. *J Neurol Sci* 1995; **134**: 41-46 [PMID: 8747841 DOI: 10.1016/0022-510X(95)00172-9]
- 124 **Llompert-Pou JA**, Abadal JM, Güenther A, Rayo L, Martín-del Rincón JP, Homar J, Pérez-Bárcena J. Transcranial sonography and cerebral circulatory arrest in adults: a comprehensive review. *ISRN Critical Care* 2013 [DOI: 10.5402/2013/167468]
- 125 **Ducrocq X**, Braun M, Debouverie M, Junges C, Hummer M, Vespignani H. Brain death and transcranial Doppler: experience in 130 cases of brain dead patients. *J Neurol Sci* 1998; **160**: 41-46 [PMID: 9804115 DOI: 10.1016/S0022-510X(98)00188-9]
- 126 **Poularas J**, Karakitsos D, Kouraklis G, Kostakis A, De Groot E, Kalogeromitros A, Bilalis D, Boletis J, Karabinis A. Comparison between transcranial color Doppler ultrasonography and angiography in the confirmation of brain death. *Transplant Proc* 2006; **38**: 1213-1217 [PMID: 16797266 DOI: 10.1016/j.transproceed.2006.02.127]
- 127 **Monteiro LM**, Bollen CW, van Huffelen AC, Ackerstaff RG, Jansen NJ, van Vught AJ. Transcranial Doppler ultrasonography to confirm brain death: a meta-analysis. *Intensive Care Med* 2006; **32**: 1937-1944 [PMID: 17019556 DOI: 10.1007/s00134-006-0353-9]
- 128 **Ducrocq X**, Hassler W, Moritake K, Newell DW, von Reutern GM, Shioagai T, Smith RR. Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography: Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology. *J Neurol Sci* 1998; **159**: 145-150 [PMID: 9741398 DOI: 10.1016/S0022-510X(98)00158-0]
- 129 **Wijdicks EF**. Determining brain death in adults. *Neurology* 1995; **45**: 1003-1011 [PMID: 7746373 DOI: 10.1212/WNL.45.5.1003]

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## Novel role of phosphodiesterase inhibitors in the management of end-stage heart failure

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### Abstract

In advanced heart failure (HF), chronic inotropic therapy with intravenous milrinone, a phosphodiesterase III inhibitor, is used as a bridge to advanced management

that includes transplantation, ventricular assist device implantation, or palliation. This is especially true when repeated attempts to wean off inotropic support result in symptomatic hypotension, worsened symptoms, and/or progressive organ dysfunction. Unfortunately, patients in this clinical predicament are considered hemodynamically labile and may escape the benefits of guideline-directed HF therapy. In this scenario, chronic milrinone infusion may be beneficial as a bridge to introduction of evidence based HF therapy. However, this strategy is not well studied, and in general, chronic inotropic infusion is discouraged due to potential cardiotoxicity that accelerates disease progression and proarrhythmic effects that increase sudden death. Alternatively, chronic inotropic support with milrinone infusion is a unique opportunity in advanced HF. This review discusses evidence that long-term intravenous milrinone support may allow introduction of beta blocker (BB) therapy. When used together, milrinone does not attenuate the clinical benefits of BB therapy while BB mitigates cardiotoxic effects of milrinone. In addition, BB therapy decreases the risk of adverse arrhythmias associated with milrinone. We propose that advanced HF patients who are intolerant to BB therapy may benefit from a trial of intravenous milrinone as a bridge to BB initiation. The discussed clinical scenarios demonstrate that concomitant treatment with milrinone infusion and BB therapy does not adversely impact standard HF therapy and may improve left ventricular function and morbidity associated with advanced HF.

**Key words:** Milrinone; Advanced heart failure; Bridge to beta blocker; Combination therapy; Inotrope support

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**Core tip:** Heart failure (HF) patients requiring chronic inotropic support are considered hemodynamically labile and may escape the benefits of evidence based HF therapy (HFTx). Chronic milrinone infusion may be bene-

ficial as a bridge to introduction of HFTx. We discuss evidence that intravenous milrinone support may allow introduction of beta blocker (BB). We propose that HF patients who are intolerant to BB therapy may benefit from intravenous milrinone as a bridge to BB initiation. When used together, BB mitigates cardiotoxic effects and decreases the risk of arrhythmias associated with milrinone. Whereas, milrinone does not attenuate the clinical benefits of BB therapy.

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## INTRODUCTION

Heart failure (HF) is a chronic progressive disease with high morbidity and in advanced stages with an annual mortality > 50%; and prevalence is projected to rise<sup>[1-3]</sup>. Although the long-term benefit of beta-blocker (BB) in advanced HF is well established<sup>[4]</sup>, many patients may be intolerant due to the negative hemodynamic impact of acute therapy and escape the benefits of HF therapy<sup>[4-7]</sup>. In such patients with advanced HF, chronic inotropic support is used as a bridge to transplantation, ventricular assist device, or palliation strategy for clinical and hemodynamic improvement. However, the use of chronic inotropic therapy as a bridge to introduction of HF therapy, specifically BB therapy, has not been effectively explored. Furthermore, chronic inotropic support is discouraged in advanced HF patients due to increased sudden death and accelerated disease progression<sup>[8,9]</sup>. In inotrope dependent advanced HF patients, combination therapy with intravenous milrinone infusion and BB provide a unique opportunity.

Concomitant therapy with BB and inotropes has been reported; however only type IIIA phosphodiesterase inhibitors (PDEI) such as milrinone and enoximone (an PDEI agent available in oral and intravenous formulations in Europe) have demonstrated a positive impact on hospitalization and functional status<sup>[10-15]</sup>. Both milrinone and enoximone have shown to improve left ventricular ejection fraction (LVEF) when used in combination with BBs<sup>[12,16,17]</sup>. However, latest HF management guidelines do not comment on this dual therapy approach and recommends intravenous milrinone infusion only as bridge to advanced management or palliation in refractory end-stage HF<sup>[2,18,19]</sup>.

This review discusses the beneficial effects of combining milrinone infusion and BB therapy in advanced HF. When used together, BB attenuates the cardiotoxicity and accentuates the hemodynamic effect of milrinone. Wherein, milrinone provides the hemodynamic support for introduction of BB therapy. Further, BB therapy decreases the risk of adverse arrhythmias associated with

chronic PDEI. Finally, molecular pathways supporting beneficial effects of combination therapy with milrinone infusion and BB therapy are discussed. The index cases to be discussed demonstrate improvement in LVEF after concomitant treatment with carvedilol and chronic milrinone infusion in end-stage HF with severe functional limitation.

## Intravenous milrinone therapy in HF

Intravenous milrinone is typically used in patients with acute systolic HF with signs or symptoms of end organ hypoperfusion<sup>[2,18,19]</sup>. However, inotropic support may be difficult or impossible to wean and prolonged support may be required.

The earliest use of chronic inotropic infusion as viable management option in end-stage HF patients was in 1987<sup>[20]</sup>. Mehra *et al*<sup>[21]</sup> reported a 72% survival on long-term milrinone support with a mean duration of 160 d in advanced HF patients awaiting transplantation. Brozena *et al*<sup>[22]</sup> found similar results in a study of 60 patients committed to home milrinone with an 88.3% survival rate to heart transplantation. In a prospective randomized study that included 19 hospitalized patients who received milrinone therapy, Aranda *et al*<sup>[23]</sup> showed that 84% survived to receive heart transplantation with a mean waiting of 60 ± 45 d.

In advanced HF patients who are transplant ineligible, success of long-term inotrope therapy has been modest. Harjai *et al*<sup>[24]</sup> reported a decrease in the number of hospital admissions from 2.7 ± 2.6 to 1.3 ± 1.3 ( $P = 0.056$ ) and length of hospital stay from 20.9 ± 12.7 to 5.5 ± 5.4 d ( $P = 0.0004$ ) with improvement in NYHA functional class from 4.0 ± 0.0 to 2.7 ± 0.9 ( $P < 0.0001$ ) in 24 patients with LVEF < 30%, chronic inotrope-dependence and intolerance to oral HF agents. The benefit of therapy was at the expense of eight deaths (38%) after 2.8 ± 1.7 mo of home IV inotropic therapy. Hershberger *et al*<sup>[25]</sup> showed a 3, 6 and 12 mo mortality of 51%, 26% and 6%, respectively, in 36 inotrope-dependent patients with refractory HF on high-dose milrinone (mean dose: 0.6 ± 0.3 mcg/kg per minute). Additionally, using Medicare data, Hauptman *et al*<sup>[26]</sup> reported reductions in hospital days at all time points (30, 60 and 180 d) but was negatively counterbalanced by a mortality rate exceeding 40% at 6 mo in 331 patients on chronic inotrope therapy. In a single center retrospective analysis of 56 inotrope dependent, transplant ineligible HF patients, Gorodeski *et al*<sup>[27]</sup> reported 62% mortality and 48% hospitalization during a median follow-up of 130 d. However, in a recent single center study of 197 contemporary HF patients, Hashim *et al*<sup>[28]</sup> reported an overall median survival of 18 mo on continuous inotropic therapy. Median survival was 9 mo in whom inotrope therapy was intended as palliation, with a 1-year actuarial survival of 48% and a 2-year actuarial survival of 38%. Among all patients placed on inotropes, those on milrinone had a better survival than on dobutamine. The authors proposed that the modest improvement in survival compared to prior studies may be related to



utilization of HF medical therapy and electrophysiologic devices that treat arrhythmias.

In the largest study to date, the PROMISE (Prospective Randomized Milrinone Survival Evaluation) trial randomized 1088 HF patients with NYHA functional class III or IV to placebo or oral milrinone<sup>[29]</sup>. The milrinone group had 28% higher mortality at 6 mo. However, it is noteworthy that patients did not have defibrillators, and those requiring BB were excluded. Moreover, the study did not evaluate hemodynamics at enrollment with milrinone therapy. Secondary analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study revealed a neutral to beneficial effect of milrinone on 60 d cardiovascular hospitalizations and composite of death and readmission in nonischemic cardiomyopathy but harmful effect in ischemic cardiomyopathy<sup>[30]</sup>. In addition, it is not clear whether the mortality on chronic inotropic therapy is above and beyond that of patients with end-stage HF where medical options are limited, specifically those with resting hemodynamic decompensation who are not candidates for advanced management<sup>[9]</sup>.

In the light of existing evidence (Table 1), the American Heart Association/American College of Cardiology HF management consensus guideline classifies chronic inotrope infusion in refractory HF as a class IIb indication/level of evidence B due to a lack of randomized controlled trials supporting morbidity and mortality benefits<sup>[2,18]</sup>.

### **Combination of intravenous milrinone infusion with beta-blocker**

Patients whose BB dosages have to be reduced or stopped have worse clinical outcomes than those in whom BB is maintained<sup>[31]</sup>. The use of intravenous PDEI permits successful initiation and up titration of BBs in HF patients who are intolerant to BB therapy<sup>[13,32-34]</sup>. Milrinone provides hemodynamic support by improving systolic and diastolic function, along with decreasing afterload and filling pressures, correcting some of the adverse effects of acute BB therapy<sup>[14]</sup>. Whether these hemodynamic benefits translate into clinical improvement has not been extensively studied. Kumar *et al.*<sup>[33]</sup> assessed the tolerability of carvedilol titration and ability to wean inotrope support in a retrospective review of 32 patients with HF. Seventeen patients with NYHA functional class IIIb/IV HF (group I) who received intermittent milrinone infusion were compared to 15 patients with NYHA functional class II/IIIa symptoms (group II) who did not. Both groups were started on carvedilol 3.125 mg twice daily and titrated to 25 mg twice daily every 2 wk as tolerated. Milrinone infusion had no impact on carvedilol titration (88% vs 93%). At 8 wk, 53% patients in group I were successfully weaned off milrinone infusion. Those who could not be weaned had a 50% decrease in the frequency of infusions. The majority (63%) of group I patients improved by one or more functional class at the end of follow-up. Another retrospective review assessed BB tolerability in 16 patients with stage D HF on continuous milrinone infusion<sup>[35]</sup>. Twelve patients

were started on metoprolol tartrate or carvedilol and the remaining four received only milrinone. After 6 mo, 92% of patients on milrinone were able to tolerate dual therapy with a BB. No significant changes in blood pressure and heart rate after were noted BB initiation. One patient in each group died, and rates of hospitalization for HF were similar (0.83/pt in combination group vs 0.5/pt in BB alone). While these studies suggest tolerability and symptomatic improvement with dual therapy, results cannot be unequivocally extrapolated due to the small sample sizes.

In a retrospective analysis, Zewail *et al.*<sup>[36]</sup> reported hemodynamic and clinical outcomes of long-term combination therapy with intravenous milrinone and BB in 65 patients with severe HF (NYHA class IV and LVEF < 25%) refractory to oral medical therapy. Fifty-one patients (78%) successfully tolerated BB therapy while on intravenous milrinone, while 14 patients did not and thus received milrinone monotherapy. Functional class improved from NYHA class IV to II-III with combination therapy. While no patients in the milrinone-only arm could be weaned off, 47% patients (24/51) in the combination arm were successfully weaned off. The corrected QT interval was significantly prolonged in the monotherapy group (mean  $\pm$  436  $\pm$  13 ms before vs 469  $\pm$  28 ms after;  $P$  = 0.002), whereas the interval remained unchanged in the combination group. Most notably, survival at 3 years was 59% higher in the combination group vs the milrinone monotherapy group ( $P$  < 0.001). One died of sudden cardiac death on treatment day 116 in the combination group. Jiménez *et al.*<sup>[10]</sup> carried out an observational study of 26 inotrope dependent patients (> 8 wk home inotrope support) with end stage HF, with 17 patients as bridge to transplantation and 9 patients as destination therapy. They reported an 85% survival at an average of 10 mo home inotropic therapy. The reported mortality rates in the above nonrandomized studies were consistent with randomized studies of similar HF patients<sup>[37]</sup>.

Gattis *et al.*<sup>[38]</sup> conducted a post-hoc analysis comparing patients receiving BB at the time of hospitalization to those who did not using the OPTIME-CHF study. The 949 patients with acute HF exacerbation were randomized to receive 48-72 h of intravenous milrinone vs placebo. In patients who were continued on BB on admission, there was no difference in the primary endpoint regardless of assignment to milrinone or placebo. Patients whose BB were withdrawn upon randomization to milrinone had worse outcomes (mortality 28.6% vs 7.7%,  $P$ -value not reported). Furthermore, patients who received both milrinone and BB during hospitalization had the lowest 60-d mortality (5.8%).

The findings of above studies suggest that combination therapy may reduce mortality and facilitate discontinuation of inotropic support in advanced HF. However, retrospective design and small sample sizes preclude firm conclusions on the impact of combination therapy on mortality, hospitalization, and symptomatic improvement. Further, as there is substantial evidence



Table 1 Clinical studies evaluating phosphodiesterase III inhibitors in heart failure

Ref.	Aim of study	Background beta blocker therapy	Study size n (total)	HF symptoms	Trial duration	Major findings/conclusion	Impact of therapy on LVEF	Complications/adverse events	Inotrope weaning rate
Packer <i>et al</i> <sup>[20]</sup> , 1991	Effect of oral milrinone on mortality of pts with symptomatic chronic HF on conventional therapy	No	1088	100% NYHA III-IV 42% NYHA IV	Median F/U duration 6.1 mo (stopped early due to adverse effects)	28% increased mortality with milrinone (30% <i>vs</i> 24%)	Not reported	Syncope palpitations hypotension headache blurry vision	Not reported
Böhm <i>et al</i> <sup>[16]</sup> , 1997	Metoprolol restores the reduction of the inotropic effect of the cAMP-phosphodiesterase inhibitor milrinone, independent of beta-adrenoceptor	Yes (100%)	15	NYHA II or III	6 mo	Treatment with metoprolol increased LVEF, fractional shortening and submaximal exercise tolerance and reduced heart rate, plasma norepinephrine concentrations  After metoprolol treatment, milrinone increased fractional shortening but had no effect before beta-blocker treatment  Effect of dobutamine was completely antagonized by treatment with metoprolol	Addition of metoprolol improved EF (%) from 24.6 ± 1.5 to 40.3 ± 3.6	Not reported	Not reported
Shakar <i>et al</i> <sup>[23]</sup> , 1998	Clinical impact of combined therapy with enoximone and beta blocker	Yes (80%)	30	NYHA IV	Mean duration of combination therapy was 9.4 ± 1.8 mo; mean length of F/U was 20.9 ± 3.9 mo	Combination therapy with enoximone and beta blocker improved EF and functional status in severe HF	LVEF increased from 17.7 ± 1.6% to 27.6 ± 3.4% ( <i>p</i> = 0.01) NYHA improved from 4 to 2.8 ( <i>P</i> = 0.0001)	2 sudden deaths	48% were weaned off enoximone
Yamani <i>et al</i> <sup>[67]</sup> , 2001	Clinical outcome and economic cost of dobutamine-based and milrinone-based therapy in patients with ADHF	Yes 20% (18% milrinone grp)	329 (60 milrinone grp)	100% NYHA IV	Retrospective review of ADHF admissions	No difference in the in-hospital mortality rate or clinical outcomes	Not reported	No difference in adverse effects between the grps (20% pts in milrinone grp with either NSVT or VT)	Not reported
Lowes <i>et al</i> <sup>[33]</sup> , 2001	Efficacy of milrinone <i>vs</i> dobutamine in patients with decompensated heart failure on chronic carvedilol therapy	Yes (100%)	20	100% NYHA II-IV	Acute therapy	Dobutamine has less favorable hemodynamic effects in patients treated chronically with carvedilol	Not reported	Not reported	Not reported
Kumar <i>et al</i> <sup>[33]</sup> , 2001	Carvedilol titration in NYHA class IIIb/IV on milrinone therapy as compared to class II / IIIa CHF without milrinone	Yes (90%)	32	Class II-IV	Mean: 24 wk	Successful carvedilol uptitration in NYHA III-b/IV can be achieved at similar rates as in NYHA II / IIIa in the presence of stable chronic milrinone therapy	Not reported	No statistical difference in adverse events among the two grps	53% patients were weaned off milrinone infusions in a mean of 8.4 ± 8.4 wk

Metra <i>et al</i> <sup>[13]</sup> , 2002	Hemodynamic effects of dobutamine and enoximone before and after 9-12 mo of beta-blocker therapy with metoprolol or carvedilol in chronic HF	Yes (100%)	34	NYHA II-IV	9-12 mo	Beta blockers significantly inhibit the favorable hemodynamic response to dobutamine. No attenuation occurred with beta blockers and enoximone	Not reported	Not reported	Not reported
Cuffe <i>et al</i> <sup>[68]</sup> , 2002	Short-term milrinone in addition to standard therapy to improve outcomes in pts with ADHF	Yes (22%)	949	93% NYHA III-IV	Treatment for up to 72 h, 60 d F/U	Milrinone was associated with higher rate of treatment failure at 48 h due to AE (12.6% <i>vs</i> 2.1%)	Not reported	Hypotension, (SBP < 80 mmHg); 10.7% with milrinone Significant atrial arrhythmias during index hospitalization; 4.6%	Not reported
Felker <i>et al</i> <sup>[30]</sup> , 2003	To assess the interaction between HF etiology and response to milrinone in ADHF	Yes (23%)	949	93% NYHA III-IV	Treatment up to 72 h with 60 d F/U	In ischemic HF, milrinone was associated with worse outcomes: 60 d mortality or hospitalization: 42% <i>vs</i> 36% placebo; in-hospital mortality 5% <i>vs</i> 1.6% placebo In nonischemic HF, benefit was derived from milrinone: 60 d mortality or hospitalization: 28% <i>vs</i> 35% placebo; in-hospital mortality 2.6% <i>vs</i> 3.1% placebo	Not reported	No difference in atrial or ventricular arrhythmias and hypotension in both grps	Not reported
Aranda <i>et al</i> <sup>[23]</sup> , 2003	Clinical outcomes and costs associated dobutamine <i>vs</i> milrinone in hospitalized pts awaiting cardiac transplantation	Yes (41% in dobutamine grp; 74% in milrinone grp)	36	Not reported presumably NYHA III-IV	Enrollment 17 mo	No difference between milrinone and dobutamine with respect to clinical outcomes or hemodynamic measures Beta blocker use in dobutamine grp was associated with worsened pulmonary pressures and PCWP	Not reported	No difference in death of length of hospital stay	Not reported
Brozena <i>et al</i> <sup>[21]</sup> , 2004	Feasibility and safety of continuous IV milrinone therapy administered at home in pts listed as status	Yes (73%)	60	NYHA II-III Peak VO <sub>2</sub> 11.4 mL/kg per minute	43 mo F/U	88.3% of pts underwent OHT 3.2% died before transplant	Not reported	8% hospitalized for IV line infection	1 pt weaned off based on clinical improvement
Abraham <i>et al</i> <sup>[69]</sup> , 2005	IB for heart transplant In-hospital mortality in ADHF pts receiving treatment with 1 of 4 vasoactive meds (NTC, nesiritide, milrinone, dobutamine)	Yes (56% milrinone grp)	2021 (milrinone)	100% NYHA IV	10/01-7/03	Worse inpatient mortality and longer LOS with IV inotropes	N/A	N/A	N/A
Feldman <i>et al</i> <sup>[60]</sup> , 2007	Whether low-dose oral enoximone could wean pts with end-stage HF from IV inotropic support	Yes (40%)	201	100% NYHA III-IV	26 wk	30 d after weaning, 51% of placebo pts and 61.40% enoximone pts were alive and free of IV inotropic therapy	Not reported	Dyspnea, 5% enoximone <i>vs</i> 0% placebo, <i>P</i> < 0.05	

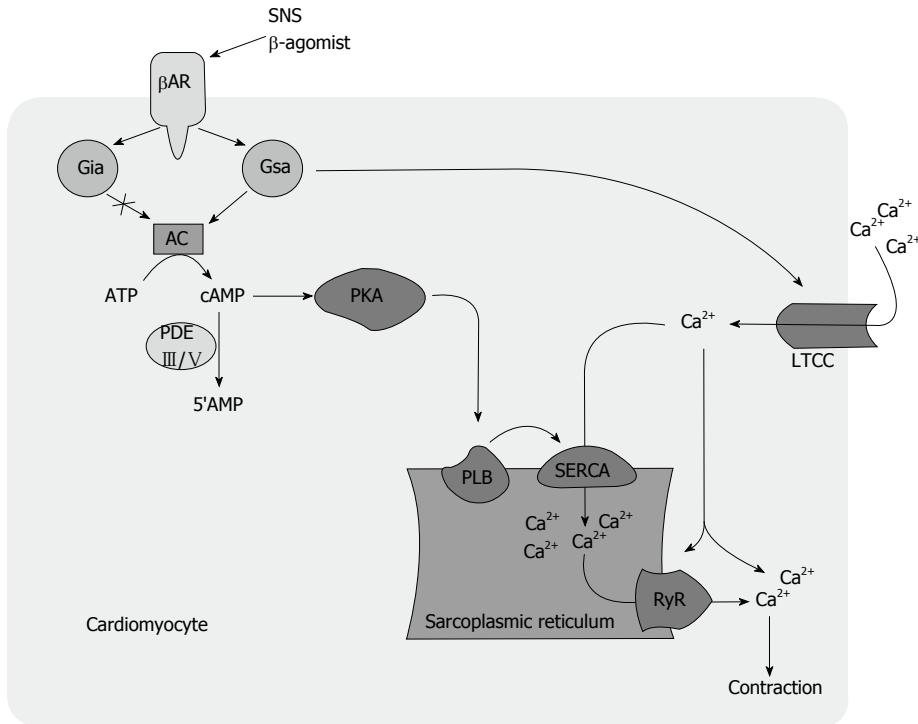
Elkayam <i>et al</i> <sup>[71]</sup> , 2007	Six month risks of all-cause mortality and all-cause mortality plus rehospitalization associated with the use of vasodilators, inotropes, and their combinations	Yes (62%)	433; 75 (vasodilator); 133 (IV inotrope); 47 (both); 178 (neither inotrope/vasodilator)	Mean peak VO <sub>2</sub> 10.0	N/A	Not reported	N/A	N/A
Gorodeski <i>et al</i> <sup>[27]</sup> , 2009	Relationship between choice of dobutamine or milrinone and mortality in inotrope dependent stage D HF pts	Yes [5% (dob) <i>vs</i> 34% (mil)]	112	Not reported presumably NYHA III-IV	Median F/U of 130 d	Not reported	Not reported	Not reported
Metra <i>et al</i> <sup>[27]</sup> , 2009	Effects of low dose enoximone on symptoms, exercise capacity, and major clinical outcomes in pts with advanced HF who were also treated with beta blockers and other guideline recommended background therapy	ESSENTIAL I Yes (83%) ESSENTIAL II Yes (90%)	ESSENTIAL I: 904 ESSENTIAL II: 950	100% NYHA III-IV	Median F/U duration 16.6 mo	Not reported	Palpitations 8% enoximone <i>vs</i> 5% placebo, <i>P</i> = 0.01	N/A

AE: Adverse event; dob: Dobutamine; F/U: Follow-up; grp: Group; HF: Heart failure; mil: Milrinone; NYHA: New York Heart Association; OPTIME-CHF: The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study; OHT: Orthotopic heart transplant; PCWP: Pulmonary capillary wedge pressure; pts: Patients; SBP: Systolic blood pressure; IV: Intravenous; cAMP: Cyclic adenosine monophosphate; ADHF: Acute decompensated heart failure; CV: Cardiovascular; LVEF: Left ventricular ejection fraction; LOS: Length of stay; EF: Ejection fraction; NSVT: Non sustained ventricular tachyarrhythmia; NTG: Nitroglycerin; VT: Ventricular tachyarrhythmia; VO<sub>2</sub>: Peak oxygen consumption; ADHERE: The Acute Decompensated Heart Failure National Registry; EMOIE: The Enoximone in intravenous inOTrope-dependent subjects study.

on BBs in mortality reduction, it would be unjustified to randomize BB vs placebo in milrinone treated patients with refractory HF. Larger observational studies would further elucidate the potential clinical benefits of combining BB with milrinone.

MOLECULAR PATHWAYS SUPPORTING COMBINATION THERAPY

Defective calcium (Ca<sup>2+</sup>) handling is thought to be a major contributor to mechanical and electrical dysfunction in HF (Figure 1)<sup>[39]</sup>. The increased mortality associated with PDEI therapy in HF is attributed to a proarrhythmic effect<sup>[29,40,41]</sup>, contributing to increased sudden cardiac death and direct cardiomyocyte toxicity related to cyclic adenosine monophosphate (cAMP) mediated Ca<sup>2+</sup> overload and sustained beta-1-receptor pathway signaling (Figure 2)<sup>[21]</sup>. Recent investigations suggest that modulation of



**Figure 1** Beta-adrenoreceptor mediated signal transduction leads to the activation of both G stimulatory alpha protein and G inhibitory alpha protein. Activated  $G_{\alpha s}$  activates adenylyl cyclase (AC) which converts ATP into cAMP while activated  $G_{\alpha i}$  inhibits AC. Activated  $G_{\alpha s}$  also leads to calcium ( $Ca^{2+}$ ) mobilization into cardiomyocyte by activating L-type calcium channel (LTCC) independent of AC. This increase in intracellular  $Ca^{2+}$  concentration leads to activation of ryanodine receptor (RyR) which causes further release of  $Ca^{2+}$  from SR, a phenomenon known as calcium-induced calcium release. Elevated cAMP activates phosphokinase A (PKA) that inhibits phospholamban (PLB) by phosphorylating it. Phosphorylation of PLB increases uptake of  $Ca^{2+}$  from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This enhanced  $Ca^{2+}$  entry into SR has positive impact on both systolic and diastolic function. In diastole, decreased intracellular  $Ca^{2+}$  causes relaxation. In systole increased release of  $Ca^{2+}$  from SR store through RyR activation increases inotropy. In the failing myocardium, chronic stimulation of  $\beta AR$  results in ineffective activation of AC, persistent activation of L-type calcium channel that increases  $Ca^{2+}$  influx, and decreased  $Ca^{2+}$  uptake into the SR due to decreased SERCA activity. This translates into systolic and diastolic dysfunction and increased arrhythmogenicity.  $\beta AR$ : Beta-adrenoreceptor; ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate;  $G_{\alpha i}$ : G inhibitory alpha protein;  $G_{\alpha s}$ : G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system.

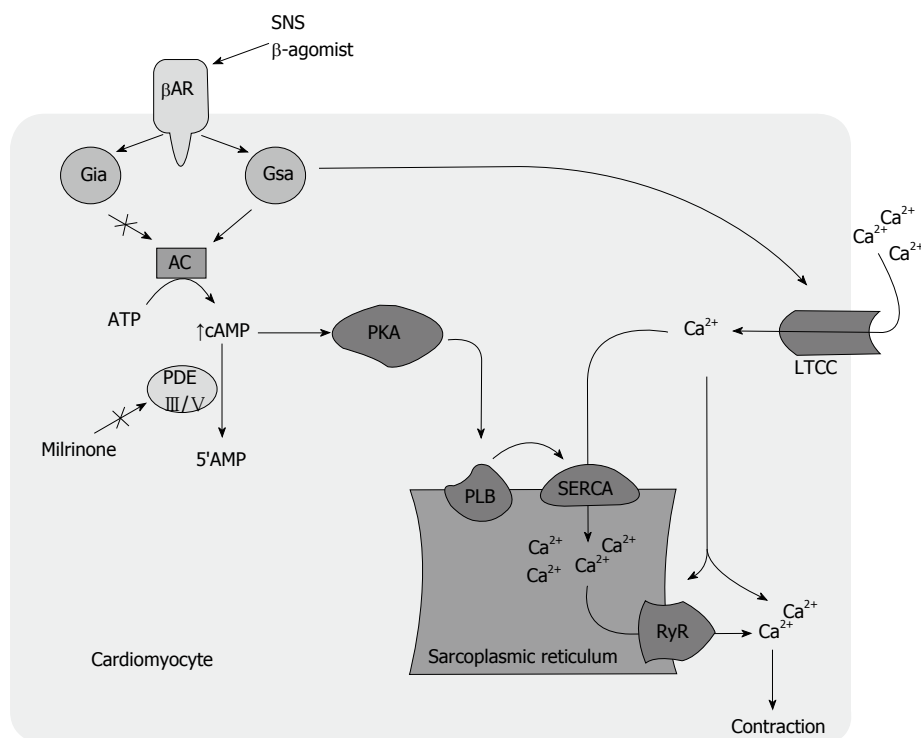
$Ca^{+}$  handling may result in improvements in inotropy and lusitropy without increasing arrhythmogenesis and cardiotoxicity<sup>[39,42-44]</sup>. BBs have shown to attenuate these molecular responses<sup>[45-48]</sup> and may attenuate adverse effects associated with PDEIs (Figure 3)<sup>[49,50]</sup>.

In the presence of BB, the harmful sustained B-receptor pathway signaling associated with HF, mediated through cAMP-independent G- $\alpha$ -stimulating protein coupling of  $Ca^{+}$  channels<sup>[51]</sup>, is eliminated. The inotropic effect of PDEIs is still maintained through the phosphorylation of phospholamban on the sarcoplasmic reticulum (SR)<sup>[52-54]</sup>. Inotropic agents that act through inhibition of phospholamban are desirable and best tolerated<sup>[14,55]</sup>. Phospholamban phosphorylation causes decreased inhibition of SR calcium ATPase (SERCA) activity, resulting in its increased SR calcium uptake in diastole and subsequent increased release in cytosol in systole for augmented myocardial performance. This, in turn, results in increased diastolic and systolic functions<sup>[14]</sup>. Improvement in  $Ca^{+}$  handling, through targeted SERCA gene expression has shown to retard development of action potential duration alternans and hence decreased arrhythmogenesis<sup>[56]</sup>. This is further supported by an improved systolic and diastolic function without increase in heart rate in phospholamban knockout models, a maneuver that mimics phospholamban phos-

phorylation<sup>[57,58]</sup>. In addition, the delivery of pseudo-phosphorylated mutant of phospholamban into sheep heart using a viral vector reversed chronic pacing induced HF<sup>[59]</sup>. On the contrary, phosphorylation of L-type  $Ca^{+}$  channel leads to an increased  $Ca^{+}$  influx during the plateau phase of the action potential, resulting in increased intracellular  $Ca^{+}$  during both diastole and systole that causes a detrimental effect on diastolic function and arrhythmogenesis<sup>[14]</sup>.

Using an extracorporeal circulation cardioplegia reperfusion model, Usta *et al.*<sup>[60]</sup> showed evidence of decreased apoptosis with low dose milrinone on *ex vivo* human right auricle cardiomyocytes compared with controls. At lower concentrations, the most likely pharmacological target of PDEI is phospholamban as both are localized to SR<sup>[61,62]</sup>. A twelve-week treatment with lower dose of enoximone ( $\leq 50$  mg three times daily) increased exercise capacity without increasing ventricular arrhythmias. This approach demonstrated favorable effects on degree of dyspnea and physician assessments of clinical status compared to placebo<sup>[61]</sup>. A contemporary observational study suggested better survival on low dose intravenous milrinone at  $0.296 \pm 0.092$  mcg/kg per minute<sup>[28]</sup>. Although the short-term benefits have been documented, long-term efficacy and safety of low-dose PDEI remains to be demonstrated in controlled





**Figure 2** Milrinone causes inhibition of phosphodiesterase III enzyme which decreases cyclic adenosine monophosphate concentration by converting later into inactive 5'adenosine monophosphate. Increased cyclic adenosine monophosphate (cAMP) activates phosphokinase A (PKA) that inhibits phospholamban (PLB) by phosphorylating it. Inhibition of PLB increases uptake of calcium ( $\text{Ca}^{2+}$ ) from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This enhanced  $\text{Ca}^{2+}$  entry into SR has positive impact on both systolic and diastolic function. During diastole, decreased cytosolic  $\text{Ca}^{2+}$  causes relaxation. During systole increased release of  $\text{Ca}^{2+}$  from SR store through ryanodine receptor (RyR) activation increases inotropy. However, unchecked chronic stimulation of beta-adrenoreceptor ( $\beta\text{AR}$ ) causes inhibition of AC through  $\text{G}_{\alpha i}$  protein and increases intracellular  $\text{Ca}^{2+}$  influx by activation of L-type calcium channel (LTCC). Activated LTCC indirectly increases intracellular  $\text{Ca}^{2+}$  through activation of RyR mediated release of  $\text{Ca}^{2+}$  from SR. This increased intracellular influx of  $\text{Ca}^{2+}$  is associated with increased arrhythmogenicity. ATP: Adenosine triphosphate;  $\text{G}_{\alpha i}$ : G inhibitory alpha protein;  $\text{G}_{\alpha s}$ : G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system.

trials. In patients with advanced HF who do not tolerate BB therapy, we choose intravenous milrinone continuous infusion at low dose ( $< 0.5 \mu\text{g/kg}$  per minute) as this strategy is shown to augment cardiac function to permit BB therapy<sup>[61]</sup>.

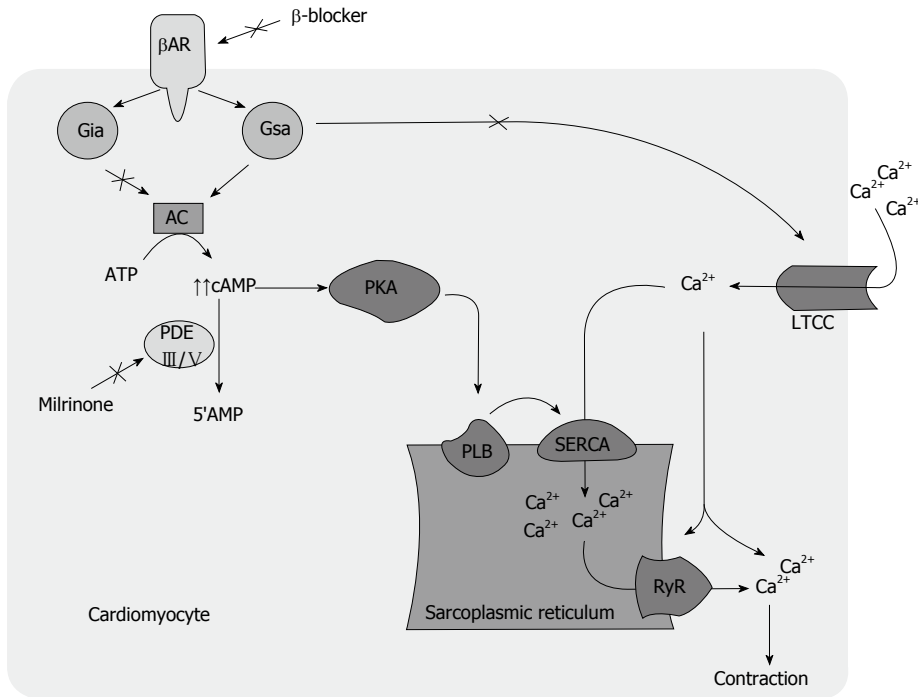
In addition, when used in combination, BB may enhance hemodynamic effects related to PDEI therapy by decreasing activity of upregulated inhibitory G-alpha-inhibitory protein activity<sup>[12,63]</sup>. The choice of BB to use in combination with a PDEI is uncertain. The use of B1-selective agent is suggested to be preferable as its blockade leads to increased B2-receptor-mediated signal transduction through cross-regulatory mechanisms<sup>[64]</sup>, which is less cardiomyopathic<sup>[65]</sup> and may even prevent apoptosis<sup>[66]</sup>. The vasodilator effect of carvedilol can be additive to that of milrinone. However, this combination may be not desirable in patients with marginal blood pressures. The vasodilator property is less pronounced and response to milrinone is not compromised by additional vasodilation once the patient becomes stable<sup>[17]</sup>.

### Clinical scenario

**Case1:** A 67-year-old man with chronic cardiomyopathy with severely reduced systolic function with LVEF  $< 15\%$  without significant epicardial coronary artery disease was impaired by six hospitalizations in five months and

New York Heart Association (NYHA) class IV functional status. Due to inability to tolerate HF medicines and inadequate diuretic response, invasive hemodynamic assessment was performed. Elevated biventricular filling pressures and decreased cardiac output were noted, both of which improved 20% after milrinone bolus ( $0.5 \text{ mcg/kg}$  per minute over 10 min) (Table 2). Due to refractory cardiomyopathy and hemodynamic findings, he was started on long-term continuous home milrinone infusion. Consequently, the patient tolerated carvedilol initiation and up-titration on outpatient follow-up. His functional class improved to NYHA class II - III and HF hospitalizations decreased to three in the subsequent nine months. Defibrillator interrogation throughout did not reveal significant arrhythmias. Nine months into treatment, LVEF improved to 35%-40% and milrinone was discontinued (Video core tip). The patient continued to thrive independent of milrinone therapy.

**Case 2:** A 50-year-old man with chronic cardiomyopathy with severely reduced LVEF 10%-15% without significant epicardial coronary artery disease was admitted for decompensated HF with acute renal insufficiency and inadequate diuretic response. Invasive hemodynamics revealed elevated biventricular pressure with severely decreased cardiac output (Table 2). Intravenous mli-



**Figure 3** Concomitant use of beta blocker and milrinone causes inhibition of G inhibitory alpha protein which is an inhibitor of adenylyl cyclase and phosphodiesterase III enzyme, both results in increased cyclic adenosine monophosphate concentration. Increased cAMP inhibits phospholamban (PLB) resulting in efficient movement of calcium ( $\text{Ca}^{2+}$ ) from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This PLB mediated  $\text{Ca}^{2+}$  handling results in improved systolic and diastolic function. In addition, BB inhibits beta-adrenoreceptor ( $\beta\text{AR}$ ) mediated increased  $\text{Ca}^{2+}$  influx through L-type calcium channel (LTCC) that is associated with increased arrhythmogenicity. ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; Gai: G inhibitory alpha protein; Gas: G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system; BB: Beta blocker; AC: Adenylyl cyclase.

**Table 2** Hemodynamic parameters at baseline and after milrinone loading

Hemodynamic parameters	Patient 1		Patient 2		Reference values
	Baseline	Post-milrinone loading	Baseline	Post-milrinone loading	
RA (mmHg)	15		15		5-7
RV (mmHg)	54/15		Dec-58		15-30/1-5
PA (mmHg)	53/33 (40)	56/21 (34)	61/37 (45)		15-30/4-10; mean < 20
PA O <sub>2</sub> saturation	49.50%		57%		60%-80%
PCWP (mmHg)	29	15	30		< 12
Cardiac output (L/min)	5.1	7.1	3.3	6	4-8
Cardiac index (L/min per meter squared)	2.1	2.95	1.64	3.03	2.6-4.2
PVR (WU)	2.68	2.16	4.54		< 3 WU
Hemoglobin (g/dL)	10.2	10.2	11.7		13.5-17.5

PA: Pulmonary artery; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; RA: Right atrial; RV: Right ventricle; WU: Wood units.

none was initiated, permitting diuresis that led to a net 40-pound weight loss during the two-week hospitalization. The patient also underwent biventricular pacemaker implantation for cardiac resynchronization therapy. Over the ensuing year post-milrinone therapy, his ambulatory status improved from < 100 feet to > 6 city blocks. Defibrillator interrogation throughout the treatment duration did not reveal significant arrhythmias. Repeat LVEF after 10 mo improved to 20%-25% (Video core tip).

## CONCLUSION

In patients with advanced HF, use of a combination

therapy with low-dose intravenous milrinone infusion and BB offers an appealing strategy. In the treatment of advanced HF, we propose that chronic milrinone infusion be regarded as a "bridge to BB" in addition to the traditional bridge to advanced options or palliation strategy. Attempt at initiation and up-titration of BBs should be underscored in such patients. Milrinone provides hemodynamic support to initiate and up-titrate BB in the presence of BB-intolerance. Moreover, dual therapy improves symptoms and decreases hospitalization. Lastly, LVEF may improve with this approach without any ill-effects and significant arrhythmias, suggesting that this is a safe and effective therapeutic strategy in advanced refractory HF. Our experience with cases discussed above

shows improvement in LVEF after concomitant use of BB and intravenous continuous low-dose milrinone. It is possible that the cases might not have been adherent to prescribed HF medications prior to use of intravenous milrinone, and the increased LVEF is purely a reflection of medical compliance. Systematic exploration involving large cohorts is required for further understanding as the population with advanced HF continues to expand.

## REFERENCES

- 1 **Bui AL**, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011; **8**: 30-41 [PMID: 21060326 DOI: 10.1038/nrcardio.2010.165]
- 2 **Heidenreich PA**, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6**: 606-619 [PMID: 23616602 DOI: 10.1161/hhf.0b013e318291329a]
- 3 **Chen-Scarabelli C**, Saravolatz L, Hirsh B, Agrawal P, Scarabelli TM. Dilemmas in end-stage heart failure. *J Geriatr Cardiol* 2015; **12**: 57-65 [PMID: 25678905 DOI: 10.11909/j.issn.1671-5411.2015.01.007]
- 4 **Krum H**, Sackner-Bernstein JD, Goldsmith RL, Kucin ML, Schwartz B, Penn J, Medina N, Yushak M, Horn E, Katz SD. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation* 1995; **92**: 1499-1506 [PMID: 7664433 DOI: 10.1161/01.cir.92.6.1499]
- 5 **Cohn JN**, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, Krueger SK, Lejemtel T, Narahara KA, Packer M, Young ST, Holcslaw TL, Lukas MA. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *J Card Fail* 1997; **3**: 173-179 [PMID: 9330125 DOI: 10.1016/S1071-9164(97)90013-0]
- 6 **Macdonald PS**, Keogh AM, Aboyoun CL, Lund M, Amor R, McCaffrey DJ. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. *J Am Coll Cardiol* 1999; **33**: 924-931 [PMID: 10091817 DOI: 10.1016/s0735-1097(98)00680-9]
- 7 Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) *Lancet* 1999; **353**: 2001-2007 [PMID: 10376614 DOI: 10.1016/s0140-6736(99)04440-2]
- 8 **Francis GS**, Bartos JA, Adatya S. Inotropes. *J Am Coll Cardiol* 2014; **63**: 2069-2078 [PMID: 24530672 DOI: 10.1016/j.jacc.2014.01.016]
- 9 **Pinney SP**, Stevenson LW. Chronic Inotropic Therapy in the Current Era: Old Wines With New Pairings. *Circ Heart Fail* 2015; **8**: 843-846 [PMID: 26374915 DOI: 10.1161/circheartfailure.115.002481]
- 10 **Jiménez J**, Jara J, Bednar B, Bauerlein J, Mallon S. Long-term (& gt; 8 weeks) home inotropic therapy as destination therapy in patients with advanced heart failure or as bridge to heart transplantation. *Int J Cardiol* 2005; **99**: 47-50 [PMID: 15721498 DOI: 10.1016/j.ijcard.2003.11.064]
- 11 **Berger R**, Strecker K, Hülsmann M, Frey B, Pacher R, Stanek B. Experience with beta-blocker therapy in patients with advanced heart failure evaluated for HTx. *J Heart Lung Transplant* 2000; **19**: 1081-1088 [PMID: 11077226 DOI: 10.1016/s1053-2498(00)00201-1]
- 12 **Shakar SF**, Abraham WT, Gilbert EM, Robertson AD, Lowes BD, Zisman LS, Ferguson DA, Bristow MR. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. *J Am Coll Cardiol* 1998; **31**: 1336-1340 [PMID: 9581729 DOI: 10.1016/s0735-1097(98)00077-1]
- 13 **Metra M**, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, Dei Cas L. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol* 2002; **40**: 1248-1258 [PMID: 12383572 DOI: 10.1016/s0735-1097(02)02134-4]
- 14 **Shakar SF**, Bristow MR. Low-level inotropic stimulation with type III phosphodiesterase inhibitors in patients with advanced symptomatic chronic heart failure receiving beta-blocking agents. *Curr Cardiol Rep* 2001; **3**: 224-231 [PMID: 11305977 DOI: 10.1007/s11886-001-0027-8]
- 15 **Hauptman PJ**, Woods D, Prirzker MR. Novel use of a short-acting intravenous beta blocker in combination with inotropic therapy as a bridge to chronic oral beta blockade in patients with advanced heart failure. *Clin Cardiol* 2002; **25**: 247-249 [PMID: 12018885 DOI: 10.1002/clc.4950250512]
- 16 **Böhm M**, Deutsch HJ, Hartmann D, Rosée KL, Stäblein A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. *J Am Coll Cardiol* 1997; **30**: 992-996 [PMID: 9316529 DOI: 10.1016/s0735-1097(97)00248-9]
- 17 **Lowes BD**, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. *Clin Cardiol* 2000; **23**: III11-III16 [PMID: 10754776 DOI: 10.1002/clc.4960231504]
- 18 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]
- 19 **Lindenfeld J**, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2010; **16**: e1-194 [PMID: 20610207 DOI: 10.1016/j.cardfail.2010.04.004]
- 20 **Applefeld MM**, Newman KA, Sutton FJ, Reed WP, Roffman DS, Talesnick BS, Grove WR. Outpatient dobutamine and dopamine infusions in the management of chronic heart failure: clinical experience in 21 patients. *Am Heart J* 1987; **114**: 589-595 [PMID: 3630900 DOI: 10.1016/0002-8703(87)90757-5]
- 21 **Mehra MR**, Ventura HO, Kapoor C, Stapleton DD, Zimmerman D, Smart FW. Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 1997; **80**: 61-64 [PMID: 9205021 DOI: 10.1016/s0002-9149(97)00284-1]
- 22 **Brozena SC**, Twomey C, Goldberg LR, Desai SS, Drachman B, Kao A, Popjes E, Zimmer R, Jessup M. A prospective study of continuous intravenous milrinone therapy for status IB patients awaiting heart transplant at home. *J Heart Lung Transplant* 2004; **23**: 1082-1086 [PMID: 15454175 DOI: 10.1016/j.healun.2003.08.017]
- 23 **Aranda JM**, Schofield RS, Pauly DF, Cleeton TS, Walker TC, Monroe VS, Leach D, Lopez LM, Hill JA. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J* 2003; **145**: 324-329 [PMID: 12595851 DOI: 10.1067/mhj.2003.50]
- 24 **Harjai KJ**, Mehra MR, Ventura HO, Lapeyre YM, Murgo JP, Stapleton DD, Smart FW. Home inotropic therapy in advanced heart failure: cost analysis and clinical outcomes. *Chest* 1997; **112**: 1298-1303 [PMID: 9367472 DOI: 10.1378/chest.112.5.1298]
- 25 **Hershberger RE**, Nauman D, Walker TL, Dutton D, Burgess D. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. *J Card Fail* 2003; **9**: 180-187 [PMID: 12815567 DOI: 10.1054/jcaf.2003.24]
- 26 **Hauptman PJ**, Mikolajczak P, George A, Mohr CJ, Hoover R, Swindle J, Schnitzler MA. Chronic inotropic therapy in end-stage heart failure. *Am Heart J* 2006; **152**: 1096.e1-1096.e8 [PMID: 17161059 DOI: 10.1016/j.ahj.2006.08.003]

- 27 **Gorodeski EZ**, Chu EC, Reese JR, Shishehbor MH, Hsieh E, Starling RC. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail* 2009; **2**: 320-324 [PMID: 19808355 DOI: 10.1161/cirheartfailure.108.839076]
- 28 **Hashim T**, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, Loyaga-Rendon RY, George JF, Acharya D. Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure. *Circ Heart Fail* 2015; **8**: 880-886 [PMID: 26179184 DOI: 10.1161/cirheartfailure.114.001778]
- 29 **Packer M**, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991; **325**: 1468-1475 [PMID: 1944425 DOI: 10.1056/nejm199111213252103]
- 30 **Felker GM**, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, Gheorghiade M, O'Connor CM. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003; **41**: 997-1003 [PMID: 12651048 DOI: 10.1016/s0735-1097(02)02968-6]
- 31 **Prins KW**, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of Beta-Blocker Withdrawal in Acute Decompensated Heart Failure: A Systematic Review and Meta-Analysis. *JACC Heart Fail* 2015; **3**: 647-653 [PMID: 26251094 DOI: 10.1016/j.jchf.2015.03.008]
- 32 **Lowes BD**, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone versus dobutamine in heart failure subjects treated chronically with carvedilol. *Int J Cardiol* 2001; **81**: 141-149 [PMID: 11744130 DOI: 10.1016/s0167-5273(01)00520-4]
- 33 **Kumar A**, Choudhary G, Antonio C, Just V, Jain A, Heaney L, Papp MA. Carvedilol titration in patients with congestive heart failure receiving inotropic therapy. *Am Heart J* 2001; **142**: 512-515 [PMID: 11526366 DOI: 10.1067/mhj.2001.117605]
- 34 **Constantinescu AA**, Caliskan K, Manintveld OC, van Domburg R, Jewbali L, Balk AH. Weaning from inotropic support and concomitant beta-blocker therapy in severely ill heart failure patients: take the time in order to improve prognosis. *Eur J Heart Fail* 2014; **16**: 435-443 [PMID: 24464574 DOI: 10.1002/ejhf.39]
- 35 **Earl GL**, Verbos-Kazanas MA, Fitzpatrick JM, Narula J. Tolerability of beta-blockers in outpatients with refractory heart failure who were receiving continuous milrinone. *Pharmacotherapy* 2007; **27**: 697-706 [PMID: 17461705 DOI: 10.1592/phco.27.5.697]
- 36 **Zewail AM**, Nawar M, Vrtovec B, Eastwood C, Kar MN, Delgado RM. Intravenous milrinone in treatment of advanced congestive heart failure. *Tex Heart Inst J* 2003; **30**: 109-113 [PMID: 12809251]
- 37 **Metra M**, Eichhorn E, Abraham WT, Linseman J, Böhm M, Corbalan R, DeMets D, De Marco T, Elkayam U, Gerber M, Komajda M, Liu P, Mareev V, Perrone SV, Poole-Wilson P, Roecker E, Stewart J, Swedberg K, Tendera M, Wiens B, Bristow MR. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. *Eur Heart J* 2009; **30**: 3015-3026 [PMID: 19700774 DOI: 10.1093/eurheartj/ehp338]
- 38 **Gattis WA**, O'Connor CM, Leimberger JD, Felker GM, Adams KF, Gheorghiade M. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. *Am J Cardiol* 2003; **91**: 169-174 [PMID: 12521629 DOI: 10.1016/s0002-9149(02)03104-1]
- 39 **Lou Q**, Janardhan A, Efimov IR. Remodeling of calcium handling in human heart failure. *Adv Exp Med Biol* 2012; **740**: 1145-1174 [PMID: 22453987 DOI: 10.1007/978-94-007-2888-2\_52]
- 40 **Cowley AJ**, Skene AM. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. Enoximone Investigators. *Br Heart J* 1994; **72**: 226-230 [PMID: 7946771 DOI: 10.1136/hrt.72.3.226]
- 41 **Uretsky BF**, Jessup M, Konstam MA, Dec GW, Leier CV, Benotti J, Murali S, Herrmann HC, Sandberg JA. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. Lack of benefit compared with placebo. Enoximone Multicenter Trial Group. *Circulation* 1990; **82**: 774-780 [PMID: 2144216 DOI: 10.1161/01.cir.82.3.774]
- 42 **Marks AR**. Calcium cycling proteins and heart failure: mechanisms and therapeutics. *J Clin Invest* 2013; **123**: 46-52 [PMID: 23281409 DOI: 10.1172/JCI62834]
- 43 **Bristow MR**. Treatment of chronic heart failure with  $\beta$ -adrenergic receptor antagonists: a convergence of receptor pharmacology and clinical cardiology. *Circ Res* 2011; **109**: 1176-1194 [PMID: 22034480 DOI: 10.1161/CIRCRESAHA.111.245092]
- 44 **Györke S**, Carnes C. Dysregulated sarcoplasmic reticulum calcium release: potential pharmacological target in cardiac disease. *Pharmacol Ther* 2008; **119**: 340-354 [PMID: 18675300 DOI: 10.1016/j.pharmthera.2008.06.002]
- 45 **Mann DL**, Kent RL, Parsons B, Cooper G. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation* 1992; **85**: 790-804 [PMID: 1370925 DOI: 10.1161/01.cir.85.2.790]
- 46 **Shivalkar B**, Van Loon J, Wieland W, Tjandra-Maga TB, Borgers M, Plets C, Flameng W. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. *Circulation* 1993; **87**: 230-239 [PMID: 8419012 DOI: 10.1161/01.cir.87.1.230]
- 47 **Kendall MJ**, Lynch KP, Hjalmarson A, Kjekshus J. Beta-blockers and sudden cardiac death. *Ann Intern Med* 1995; **123**: 358-367 [PMID: 7625625 DOI: 10.7326/0003-4819-123-5-199509010-00007]
- 48 **Mochizuki M**, Yano M, Oda T, Tateishi H, Kobayashi S, Yamamoto T, Ikeda Y, Ohkusa T, Ikemoto N, Matsuzaki M. Scavenging free radicals by low-dose carvedilol prevents redox-dependent  $\text{Ca}^{2+}$  leak via stabilization of ryanodine receptor in heart failure. *J Am Coll Cardiol* 2007; **49**: 1722-1732 [PMID: 17448375 DOI: 10.1016/j.jacc.2007.01.064]
- 49 **Gilbert EM**, Olsen SL, Renlund DG, Bristow MR. beta-adrenergic receptor regulation and left ventricular function in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993; **71**: 23C-29C [PMID: 8096672 DOI: 10.1016/0002-9149(93)90083-o]
- 50 **Bristow MR**. Changes in myocardial and vascular receptors in heart failure. *J Am Coll Cardiol* 1993; **22**: 61A-71A [PMID: 8397233 DOI: 10.1016/0735-1097(93)90465-d]
- 51 **Lader AS**, Xiao YF, Ishikawa Y, Cui Y, Vatner DE, Vatner SF, Homcy CJ, Cantiello HF. Cardiac G $\alpha$  overexpression enhances L-type calcium channels through an adenylyl cyclase independent pathway. *Proc Natl Acad Sci USA* 1998; **95**: 9669-9674 [PMID: 9689139 DOI: 10.1073/pnas.95.16.9669]
- 52 **Hoepfer MM**, Boeker KH. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335**: 1538 [PMID: 8927102 DOI: 10.1056/nejm199611143352017]
- 53 **Travill CM**, Pugh S, Noble ML. The inotropic and hemodynamic effects of intravenous milrinone when reflex adrenergic stimulation is suppressed by beta-adrenergic blockade. *Clin Ther* 1994; **16**: 783-792 [PMID: 7859237]
- 54 **Galie N**, Branzi A, Magnani G, Melandri G, Caldarera I, Rapezzi C, Grattoni C, Magnani B. Effect of enoximone alone and in combination with metoprolol on myocardial function and energetics in severe congestive heart failure: improvement in hemodynamic and metabolic profile. *Cardiovasc Drugs Ther* 1993; **7**: 337-347 [PMID: 8364004 DOI: 10.1007/bf00880157]
- 55 **Bristow MR**, Shakar SF, Linseman JV, Lowes BD. Inotropes and beta-blockers: is there a need for new guidelines? *J Card Fail* 2001; **7**: 8-12 [PMID: 11605160 DOI: 10.1054/jcaf.2001.26655]
- 56 **Cutler MJ**, Wan X, Laurita KR, Hajjar RJ, Rosenbaum DS. Targeted SERCA2a gene expression identifies molecular mechanism and therapeutic target for arrhythmogenic cardiac alternans. *Circ Arrhythm Electrophysiol* 2009; **2**: 686-694 [PMID: 19948504 DOI: 10.1161/circep.109.863118]
- 57 **Luo W**, Grupp IL, Harrer J, Ponniah S, Grupp G, Duffy JJ, Doetschman T, Kranias EG. Targeted ablation of the phospholamban gene is associated with markedly enhanced myocardial contractility and loss of beta-agonist stimulation. *Circ Res* 1994; **75**: 401-409 [PMID: 8062415 DOI: 10.1161/01.res.75.3.401]
- 58 **del Monte F**, Harding SE, Dec GW, Gwathmey JK, Hajjar RJ. Targeting phospholamban by gene transfer in human heart failure.



- Circulation* 2002; **105**: 904-907 [PMID: 11864915 DOI: 10.1161/hc0802.105564]
- 59 **Kaye DM**, Preovolos A, Marshall T, Byrne M, Hoshijima M, Hajjar R, Mariani JA, Pepe S, Chien KR, Power JM. Percutaneous cardiac recirculation-mediated gene transfer of an inhibitory phospholamban peptide reverses advanced heart failure in large animals. *J Am Coll Cardiol* 2007; **50**: 253-260 [PMID: 17631218 DOI: 10.1016/j.jacc.2007.03.047]
  - 60 **Usta E**, Mustafi M, Scheule AM, Ziemer G. Suppressing apoptosis with milrinone simulating extracorporeal circulation: a pilot study. *Thorac Cardiovasc Surg* 2010; **58**: 285-290 [PMID: 20680905 DOI: 10.1055/s-0030-1249925]
  - 61 **Lowes BD**, Higginbotham M, Petrovich L, DeWood MA, Greenberg MA, Rahko PS, Dec GW, LeJemtel TH, Roden RL, Schleman MM, Robertson AD, Gorczynski RJ, Bristow MR. Low-dose enoximone improves exercise capacity in chronic heart failure. Enoximone Study Group. *J Am Coll Cardiol* 2000; **36**: 501-508 [PMID: 10933364 DOI: 10.1016/s0735-1097(00)00759-2]
  - 62 **Dage RC**, Okerholm RA. Pharmacology and pharmacokinetics of enoximone. *Cardiology* 1990; **77** Suppl 3: 2-13; discussion 27-33 [PMID: 2148277 DOI: 10.1159/000174664]
  - 63 **Sigmund M**, Jakob H, Becker H, Hanrath P, Schumacher C, Eschenhagen T, Schmitz W, Scholz H, Steinfath M. Effects of metoprolol on myocardial beta-adrenoceptors and Gi alpha-proteins in patients with congestive heart failure. *Eur J Clin Pharmacol* 1996; **51**: 127-132 [PMID: 8911876 DOI: 10.1007/s002280050172]
  - 64 **Hall JA**, Ferro A, Dickerson JE, Brown MJ. Beta adrenoreceptor subtype cross regulation in the human heart. *Br Heart J* 1993; **69**: 332-337 [PMID: 8098220 DOI: 10.1136/hrt.69.4.332]
  - 65 **Liggett SB**, Tepe NM, Lorenz JN, Canning AM, Jantz TD, Mitarai S, Yatani A, Dorn GW. Early and delayed consequences of beta(2)-adrenergic receptor overexpression in mouse hearts: critical role for expression level. *Circulation* 2000; **101**: 1707-1714 [PMID: 10758054 DOI: 10.1161/01.CIR.101.14.1707]
  - 66 **Communal C**, Singh K, Sawyer DB, Colucci WS. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. *Circulation* 1999; **100**: 2210-2212 [PMID: 10577992 DOI: 10.1161/01.CIR.100.22.2210]
  - 67 **Yamani MH**, Haji SA, Starling RC, Kelly L, Albert N, Knack DL, Young JB. Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: Hemodynamic efficacy, clinical outcome, and economic impact. *Am Heart J* 2001; **142**: 998-1002 [PMID: 11717603 DOI: 10.1067/mhj.2001.119610]
  - 68 **Cuffe MS**, Califf RM, Adams KF, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002; **287**: 1541-1547 [PMID: 11911756 DOI: 10.1001/jama.287.12.1541]
  - 69 **Abraham WT**, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, Cheng ML, Wynne J. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46**: 57-64 [PMID: 15992636 DOI: 10.1016/j.jacc.2005.03.051]
  - 70 **Feldman AM**, Oren RM, Abraham WT, Boehmer JP, Carson PE, Eichhorn E, Gilbert EM, Kao A, Leier CV, Lowes BD, Mathier MA, McGrew FA, Metra M, Zisman LS, Shakar SF, Krueger SK, Robertson AD, White BG, Gerber MJ, Wold GE, Bristow MR. Low-dose oral enoximone enhances the ability to wean patients with ultra-advanced heart failure from intravenous inotropic support: results of the oral enoximone in intravenous inotrope-dependent subjects trial. *Am Heart J* 2007; **154**: 861-869 [PMID: 17967591 DOI: 10.1016/j.ahj.2007.06.044]
  - 71 **Elkayam U**, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, Young JB, Rayburn BK, Rogers JG, DeMarco T, Leier CV. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J* 2007; **153**: 98-104 [PMID: 17174645 DOI: 10.1016/j.ahj.2006.09.005]

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## Takotsubo syndrome: Advances in the understanding and management of an enigmatic stress cardiomyopathy

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### Abstract

Takotsubo cardiomyopathy is a syndrome mimicking an

acute myocardial infarction in absence of obstructive epicardial coronary artery disease to explain the degree of the wall motion abnormalities. Typically more common in the elderly women, this condition is usually triggered by unexpected emotional or physical stress situations, and is associated with electrocardiogram abnormalities and slight elevation of cardiac biomarkers. The pathophysiological mechanism is not clear yet, but it is believed that a high circulating concentration of catecholamines causes an acute dysfunction of the coronary microcirculation and metabolism of cardiomyocytes, leading to a transient myocardial stunning. Typically, it presents with acute left ventricular systolic dysfunction that in most cases is completely resolved at short term. Recurrences are rare and it is thought that the long-term prognosis is good. We present here a review of the clinical features, pathophysiology and management of this enigmatic condition.

**Key words:** Takotsubo cardiomyopathy; Stress; Review; Myocardial stunning; Left ventricle systolic dysfunction

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**Core tip:** Takotsubo cardiomyopathy is a syndrome mimicking an acute myocardial infarction in absence of obstructive epicardial coronary artery disease to explain the degree of the wall motion abnormalities. Typically more common in the elderly women, this condition is usually triggered by unexpected emotional or physical stress situations, and presents with acute left ventricular systolic dysfunction that in most cases is completely resolved at short term. Recurrences are rare and it is thought that the long-term prognosis is good. We present here a review of the clinical features, pathophysiology and management of this enigmatic condition.

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## INTRODUCTION

Takotsubo cardiomyopathy (TTC) was first described in Japan at the beginning of 90's<sup>[1]</sup>. Patients with this condition present signs and symptoms resembling those with an acute coronary syndrome (ACS), but the angiographic appearance of the epicardial coronary arteries do not explain neither the grade of the left ventricle systolic dysfunction (LVSD) nor the wall motion abnormalities typically observed in this syndrome<sup>[2]</sup>. The term "takotsubo" was used to remind the octopus trap form of the left ventricle during systole in the acute phase of disease, as result of the wall motion abnormalities in the mid-apical segments with hyperkinetic motion of the base. Along the first years of its description, it was observed that most affected people were postmenopausal women after suffering a stress situation. However, cases in men and young people have been progressively reported. Although the left ventricle mid-apical dysfunction is the pattern most frequently found, transient abnormalities in other myocardial segments have been described, such as mid-ventricular and "inverted" forms. On the other hand, there is a significant percentage of patients in whom a trigger is not identified. Therefore, currently it is recognized that TTC is a multifaceted disease with a wide spectrum<sup>[3]</sup>.

Many names have been used for calling this syndrome, including stress cardiomyopathy, transient apical dyskinesia, broken heart syndrome, apical ballooning or transient cardiomyopathy, but a consensus to define an universal name is lacking. Due to different forms of presentation, it seems more appropriate to use the term "takotsubo cardiomyopathy"<sup>[4]</sup>. Recently, it has been proposed include TTC as part of the so-called syndrome of "acute myocardial infarction without obstructive coronary atherosclerosis"<sup>[5]</sup>.

Throughout this review, based in our experience and that of the other authors, we will discuss the clinical, epidemiological and electrocardiographic features of this syndrome with an approach to the pathophysiological hypotheses and advances in the understanding of this enigmatic disease.

## CLINICAL FEATURES AND EPIDEMIOLOGY

TTC has been increasingly recognized along last two decades<sup>[6-8]</sup>, but it is still a rare condition. The true incidence of this syndrome is unknown. Several studies have estimated an incidence ranging 1.2%-2% among patients undergoing coronary angiography with a presumptive diagnosis of ACS<sup>[9,10]</sup>. Near 90% of patients with TTC are women, most of them at postmenopausal period

with a mean age around 70 years<sup>[11]</sup>. Hypertension is the predominant cardiovascular risk factor (CVRF), while prevalence of diabetes is low<sup>[12]</sup>, specially compared with those patients with ACS in whom diabetes is present at least as twice (30%)<sup>[13]</sup>. In Spain, most patients with TTC have no more than 2 CVRF (68.7%)<sup>[14]</sup>. The high predominance of female gender and the cardiovascular risk profile support the notion that coronary atherosclerosis in this syndrome does not seem to play a key role in the primary mechanisms, as in fact it happens in ACS.

Regarding clinical picture, chest pain is the most common presentation symptom, affecting 54%-80% of patients, followed by dyspnea<sup>[14-18]</sup>; among patients presenting with chest pain, typical rest angina is by far the most common symptom (59%)<sup>[14]</sup>. A triggering factor can be identified in 70%-86% of cases, being the distribution between emotional and physical stressful situations very variable among different case series studies. Within emotional triggers, the unexpected death of a loved one and family matters are very frequent, while severe acute illness and post-operative states are very common within physical triggers<sup>[14,18]</sup>. Psychological factors may play a key role in the triggering mechanisms of TTC. A high prevalence of psychiatric disorders (acute or chronic) has been recently reported, being the affective disorders, specially depression and chronic anxiety, a common finding<sup>[18,19]</sup>. TTC patients suffer psychiatric disorders more than twice than patients with ACS. These observations may lead to propose the chronic affective disorders as predisposing factors to develop TTC.

Of note, some epidemiological features such as the incidence, the most prevalence in women, the average age around 70 years, the low prevalence of diabetes, and the chest pain as the most common symptom are concordant between the published series along worldwide (Table 1). However, concerning other epidemiological data such as frequency of triggering factors, differences between those emotional and physical triggers, and incidence of specific electrocardiographic (ECG) abnormalities are very variable, which might suggest some ethnic variations of the disease or a more aggressive diagnostic approach in some countries.

Some study has found a relation between seasonal variation and incidence of TTC, with a higher frequency in winter<sup>[16]</sup>, but this finding has not been confirmed in other series<sup>[14]</sup>. Typically, TTC mimics an anterior-ST-segment elevation myocardial infarction (STEMI); some of the main clinical differences between these are listed in Table 2.

## PATHOPHYSIOLOGY

Different hypotheses have been proposed to explain the pathophysiological mechanisms in TTC, but no one seems to be conclusive<sup>[9]</sup>. Studies in animals and humans using cardiac magnetic resonance (CMR), nuclear testing, endomyocardial biopsy, advanced echocardiography

**Table 1** Epidemiological and clinical features of takotsubo cardiomyopathy

	Tsuchihashi <i>et al.</i> <sup>[15]</sup>	Núñez <i>et al.</i> <sup>[14]</sup>	Kurowski <i>et al.</i> <sup>[13]</sup>	Eshtehardi <i>et al.</i> <sup>[16]</sup>	Parodi <i>et al.</i> <sup>[11]</sup>	Ahmed <i>et al.</i> <sup>[17]</sup>	Templin <i>et al.</i> <sup>[18]</sup>
Country	Japan	Spain	Germany	Swiss	Italy	United States	Europe and United States
Year of publication	2001	2015	2007	2009	2007	2013	2015
Subjects, <i>n</i>	88	202	35	41	36	620 (systematic review)	1750 (international registry)
Age (yr)	67 ± 13	70 ± 12.5	72 ± 9	65 ± 11	75 ± 7	67	66.8 ± 13
In percentage (%)							
Reported incidence <sup>1</sup>	---	1.2	1.2	1.7	2	---	---
Women	86	90	94	85	100 <sup>6</sup>	91	89.8
Hypertension	48	67	74	56	50	---	65
Diabetes	12	15	23	5	5.5	---	14
Hyperlipidemia	24	41	34	39	39	---	31
Current smoking	---	15	20	27	19	---	20
Apical type	100 <sup>3</sup>	---	60	---	---	---	81.7
Emotional/psychological trigger	20	50	43	46	---	41	27.7
Physical (acute diseases, exercise, surgery and medical procedures) trigger	53	20	43	17	---	45	36
No identified triggering factor	26	27	14	37	28	14	28.5
Chest pain	67	80	---	76	100 <sup>2</sup>	54	76
Dyspnea	7	45	---	24	---	26	47
Syncope	---	9	---	---	---	---	7.7
ST segment elevation	90	62	69	39	100 <sup>2</sup>	39	43.7
T wave inversion	97	94.4	---	46	---	31	41 <sup>5</sup>
In hospital mortality	1	2.4 <sup>4</sup>	9	0	---	4	4.1
Long term mortality from all causes	---	---	8.6 (at 12 mo)	2 (23 ± 10 mo)	3 (at 6 mo)	---	5.6 (per patient-year)
Recurrences	2.7	0	6	5	---	---	1.8 (per patient-year)

<sup>1</sup>Incidence is based on patients with acute coronary syndrome; <sup>2</sup>This case series included only patients with chest pain and ST segment elevation; <sup>3</sup>Included only the typical form (apical ballooning); <sup>4</sup>All from noncardiac causes; <sup>5</sup>On admission; <sup>6</sup>Only included women.

techniques, biochemical testing, intracoronary imaging, physiological studies of coronary microcirculation and pharmacological tests have attempted to elucidate the origin of the ventricular dysfunction and the selective impairment of myocardial segments without reaching a definitive conclusion. TTC is an enigmatic disease and very little is known yet about its primary mechanism.

The cause seems to be multifactorial and probably a single way is not enough to explain all findings. However, it is accepted that an intense release of catecholamines could be the initial trigger that finally leads to myocardial stunning, although the mechanisms that occur into the halfway are not clear yet.

A significant proportion of TTC patients have a stressor condition (emotional or physical) shortly before the appearance of symptoms. On the other hand, patients with pheochromocytoma are susceptible to suffer similar cardiomyopathy during catecholamine crisis<sup>[20-22]</sup>. Together, those observations suggest an exaggerated response of the sympathetic system, causing a high serum catecholamine levels that initiate the cascade of events that ultimately hit the cardiomyocytes. In fact, higher levels of catecholamines have been demonstrated in TTC compared with ACS<sup>[23]</sup>. Moreover, the absence of permanent late gadolinium enhancement on CMR and the complete recovery of the ventricular dysfunction

support the myocardial-stunning phenomenon in TTC patients.

One of the first hypotheses, which emerged after ruling out obstructive coronary artery disease, was the spasm of multiple epicardial coronary arteries triggered by high levels of catecholamines<sup>[1]</sup>. This theory has not been demonstrated or reproduced reliably<sup>[24]</sup>. Attempts to induce vasospasm with acetylcholine in patients with TTC have been successful in a proportion of patients that is not enough to draw definitive conclusions<sup>[25]</sup>. Also, it is well known that some patients with definitive TTC have shown persistent ST-segment elevation without simultaneous evident coronary spasm at the angiography. Furthermore, a significant proportion of patients does not report symptoms such as chest pain or syncope that would be expected to find if epicardial coronary vasospasm would be involved.

The rupture of an atherosclerotic plaque in a long and recurrent left anterior descending (LAD) coronary artery, with thrombus formation and spontaneous lysis early aborting myocardial infarction<sup>[26]</sup>, also seems unlikely, since most patients have normal both coronary angiography and intracoronary imaging. Optical coherence tomography (OCT) have ruled out any suspicion of plaque rupture and other injuries that may go unnoticed on angiography<sup>[27]</sup>. In fact, the extent of the



**Table 2 Clinical comparison between takotsubo cardiomyopathy and STEMI**

	TTC	STEMI
Predominant gender	Women	Men
Myocardial segments involved	Extent beyond one coronary artery	Corresponding to culprit vessel
Peak of troponin	Lower	Higher
Left ventricle dysfunction recovery	Complete and at short term	Variable
Long term mortality	Lower	Higher

TTC: Takotsubo cardiomyopathy; STEMI: ST-segment elevation myocardial infarction.

left ventricle wall motion abnormalities exceeds the subtended myocardial territory of a recurrent LAD.

Myocarditis was another hypothesis. The strongest argument to rule out myocarditis is the absence of both clinical signs and permanent late enhancement on CMR demonstrated in the majority of patients with TTC.

Otherwise, nuclear studies have been of outstanding relevance to investigate the potential mechanisms at metabolic level. PET studies have found a markedly reduced uptake of F-18 fluorodeoxyglucose (an analogue of glucose) at the apical segments in patients with typical TTC<sup>[28]</sup>. Moreover, it has been found a concordance between the myocardial wall motion abnormalities and the myocardial region with an impairment of glucose uptake<sup>[13]</sup>. However, this latter seems to be more severe and extensive than the corresponding myocardial perfusion defect, which is called a mismatch between metabolism and perfusion abnormalities<sup>[29]</sup>. Similar results have been obtained with fatty acids, another energy source, in terms of reduced uptake and mismatch in the apical zone of TTC patients<sup>[30,31]</sup>. Why this reduced uptake of energy sources is produced is not well understood, but a metabolic disorder, derived from cardiomyocytes injury by the catecholamines storm probably plays a key role in the mechanisms of TTC, causing a metabolically stunned myocardium.

On the other hand, coronary microvascular dysfunction (CMD) has been strongly highlighted as a key pathophysiologic mechanism. A decreased coronary flow velocity reserve and a short diastolic deceleration time, measured with intracoronary Doppler, have been found in TTC patients<sup>[32]</sup>. These findings have been supported by non-invasive studies, such as the assessment of coronary flow reserve through transthoracic Doppler, finding that in TTC patients, there is a transient impairment of the microcirculation at the acute phase, demonstrated by a reduced CFR<sup>[33]</sup>. Other studies have documented indirect signs of CMD, such as abnormal myocardial blush grade and TIMI frame count<sup>[13,34-36]</sup>. Such abnormalities have been found not only in the LAD subtended myocardial territory but also in the other main epicardial vessels, which may suggest that CMD may occur at multivessel level. Therefore, it seems that the coronary microvascular integrity is impaired, but what is not clear yet is if myocardial stunning is consequence of

metabolic disorder or CMD<sup>[23]</sup>. Another relevant question is why other people subjected to stress conditions do not develop this syndrome. Some argue that TTC patients are unprotected at molecular level to facing the acute storm of catecholamines within context of stress situation. Recently, d'Avenia *et al.*<sup>[37]</sup> have found that mutation of BAG3, a gene involved in the epinephrine-induced apoptosis of altered cardiomyocytes, may play a role in the impaired response of myocardium to supraphysiological levels of catecholamines.

There are many questions still unanswered. Nowadays, we do not know for sure why this disease predominantly affects postmenopausal women, but epidemiological data invite us to think that estrogens in women may play a protective role. Why the left ventricle apical segments are the most affected and why the basal segments behave hyperkinetic are issues not clearly answered today, but it is believed that heterogeneous distribution and variable response of beta-receptors along myocardial segments are involved<sup>[38,39]</sup>.

Based on the myocardial dysfunction beyond one single coronary artery and the absence of concordant abnormalities in the epicardial arteries, the mechanism of myocardial stunning in TTC seems to overstep the frontiers of the epicardial coronary vessels, which lead us to search the cause in the coronary microcirculation or even at a molecular level.

## DIAGNOSIS

Typical form of TTC affects the mid and apical segments of the left ventricle with compensatory hyperkinesis of the basal segments, but in any case, the myocardial wall motion abnormalities extend more than a single epicardial coronary artery distribution. Unlike what happens in ACS, the peak of troponin in TTC is disproportionately lower compared to the extent of the myocardial dysfunction. Ruling out severe obstructive coronary artery disease and acute plaque rupture must be a priority before diagnosing this syndrome. Currently, it is recognized that TTC is, by definition, a completely reversible disease. So, it is mandatory to confirm a full recovery of the ventricular wall motion abnormalities along follow-up. Table 3 shows the most recognized diagnosis criteria for this syndrome<sup>[15]</sup>.

## VARIANTS

The left ventricular dysfunction in TTC includes not only the classical apical ballooning form but also different angiographic patterns that have been increasingly reported along last decade (Figure 1). The "mid-ventricular shape" respects both the apex and base<sup>[40]</sup>. The "reversed takotsubo", in which there are wall motion abnormalities of the base and mid segments with preserved motion/hyperkinesis of the apex, is very rare<sup>[41]</sup>. Furthermore, some case reports have documented simultaneous abnormalities at both left and right ventricles up to in third of cases<sup>[42-44]</sup>, but the isolated involvement of the

**Table 3** Diagnosis criteria for takotsubo cardiomyopathy

Patients must satisfy all the following	
ECG	New abnormalities: ST-segment elevation and or T waves inversion
Blood test	Modest peak of troponin
Imaging	Transient wall motion abnormalities (with or without apical involvement) that extend beyond a single epicardial coronary artery
Angiography	Normal or near normal epicardial coronary arteries and no evidence of plaque rupture
Excluding other diseases	Pheochromocytoma, myocarditis

Based on Mayo Clinic Criteria (2008). ECG: Electrocardiographic.

right ventricle is very uncommon<sup>[45,46]</sup>. Recently, it was described the first case of “double takotsubo”, in which the typical pattern was followed by the reversed type<sup>[47]</sup>. Thus, TTC may hit different myocardial walls, but in any case, this extends beyond a single epicardial coronary artery.

## IMAGING TECHNIQUES IN TTC

### Two-dimensional echocardiogram

This is an imperative imaging technique in the course of diagnosis and follow-up of TTC patients. Due to its ready availability, two-dimensional echocardiogram allows quantify the severity of the LVSD from the onset, which is usually not achieved with other imaging technique by time availability. This is key for supporting diagnosis, taking into account that sometimes the wall motion abnormalities improve very quickly (in some cases, it have been reported a complete recovery in less than 48 h)<sup>[48,49]</sup>. Dynamic left ventricular outflow tract obstruction (DLVOTO) due to systolic anterior motion (SAM) of mitral valve and intracavitary thrombi (mainly in the apex) are complications that can be early detected by this imaging technique, which determine specific strategies of treatment<sup>[50]</sup>. Moreover, advanced echocardiographic techniques, such as speckle-tracking and coronary flow assessment with transthoracic Doppler, are providing pathophysiologic insights about this syndrome<sup>[51]</sup>.

### Cardiac catheterization

Coronary angiography is warranted to exclude severe obstructive coronary disease as the cause of ventricular dysfunction. However, it is important to note that the presence of coronary atherosclerosis not exempt TTC. Indeed, near to 15% of patients has coronary artery disease<sup>[7,18]</sup>. Intracoronary imaging techniques, such as OCT, have been useful to definitively rule-out structural abnormalities in the epicardial vessels that may go unnoticed on angiography, including plaque rupture, eroded intimae, dissections or residual thrombus, supporting the need for searching an alternative pathophysiological mechanisms<sup>[27]</sup>. Left ventriculography has been traditionally used to describe the pattern of TTC (Figure 1).

## CMR

This imaging technique has become an important tool to advance in understanding the pathophysiological mechanisms involved in TTC. The main contribution has been the demonstration of transient myocardial edema, mainly at the apex, which is related to the degree of ventricular dysfunction, even with the repolarization electrocardiographic abnormalities<sup>[52-56]</sup>. T2-weighted imaging has shown a non-coronary distributed apical edema without contrast enhancement, which confirms that myocardial abnormalities extend beyond one single coronary artery. In clinical practice CMR is key to exclude other differential diagnosis, such as myocarditis<sup>[57]</sup>. Recently, it has been found with CMR a profound diastolic dysfunction in the acute phase, that takes more time to resolve compared with the rapid recovery of the left ventricular systolic dysfunction<sup>[58]</sup>.

**Nuclear imaging:** Single-photon emission computed tomography and positron emission tomography (PET) allow a precise assessment of myocardial perfusion and metabolism, ventricular function and even sympathetic innervations of the heart by using different radiotracers<sup>[59,60]</sup>. This techniques have been mainly used to study the pathophysiological mechanisms involved in TTC, showing that coronary flow reserve and myocardial blood flow are globally impaired, not only restricted to the dysfunctional segments, indicating a microcirculatory dysfunction at least in the acute phase<sup>[61]</sup>.

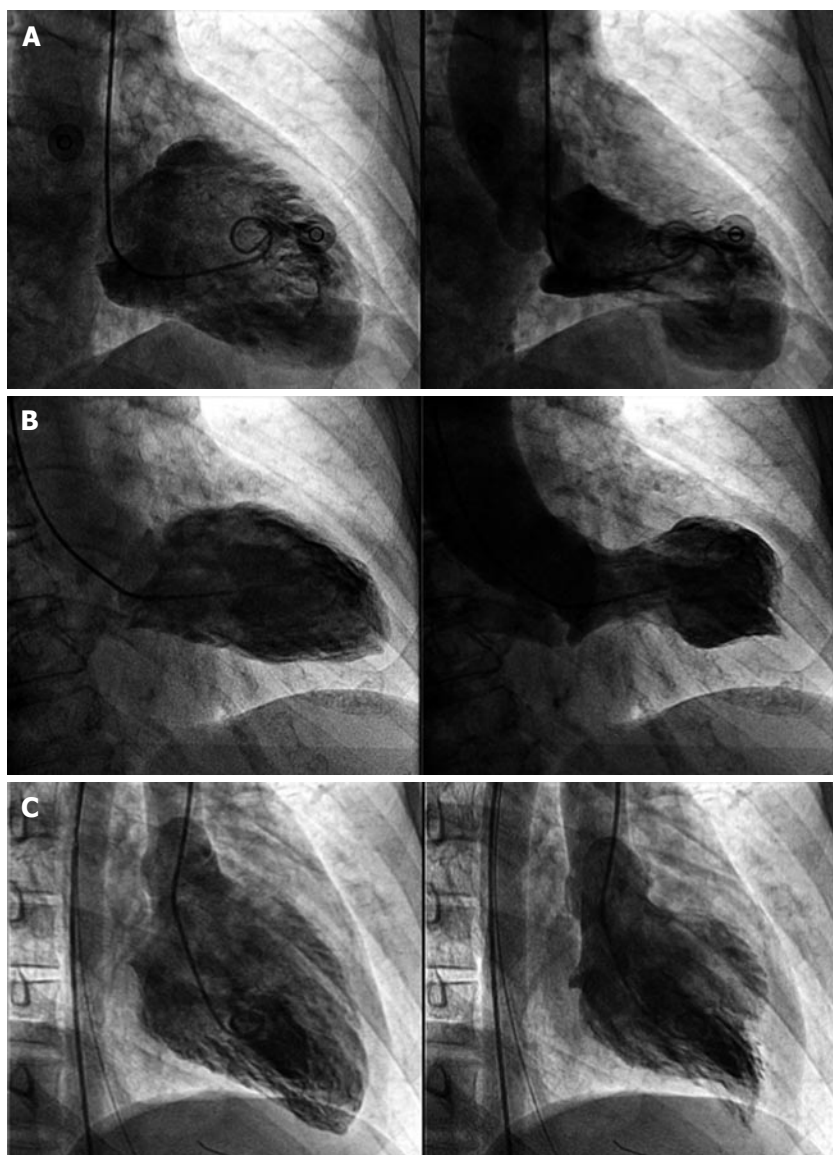
## ELECTROCARDIOGRAPHIC FEATURES OF TTC

### T waves

In our experience, up to 90% of patients develop T waves inversion at some point of evolution. This is frequently seen from the onset (38.8%), either as single finding or with ST-segment abnormalities, but they typically appear when ST-segment begins to normalize. Compared with anterior-STEMI, negative T waves in TTC are usually deeper, wider and more diffuse, affecting a greater number of leads. In patients with inverted T waves from the onset without ST-segment elevation, the absence of negative T waves on V1 and positive T waves on aVR should raise suspicion of TTC<sup>[62]</sup>. T waves inversion is less frequently found on atypical forms<sup>[63]</sup>.

### ST-segment abnormalities and comparison with AMI

ST-segment elevation is the second most common finding observed in our large registry (62%)<sup>[14]</sup>. However, as it can be seen on Table 1, there is a different incidence along worldwide, which may be explained by ethnic variations or a more aggressive diagnostic approach in some countries<sup>[64]</sup>. Because the apical region of the left ventricle is the most affected, the ST-segment elevation is more frequently found on the LAD subtended myocardial territories<sup>[65]</sup>, while it is uncommon in V1 because the right ventricle is respected mostly times. On the other



**Figure 1 Left ventriculography showing different types of takotsubo cardiomyopathy.** A: Takotsubo cardiomyopathy (TTC) typical form. On systole the left ventricle presents akinesis of the apex and hyperkinesis of the basal segments; B: Mid-ventricular variant. On systole the mid-segments are akinetic while the apical and basal segments are normal; C: "Inverted TTC". Basal and mid-segments are akinetic on systole while the apex is hyperkinetic.

hand, ST-segment reciprocal depression in the inferior leads is uncommon compared with anterior-STEMI<sup>[66]</sup>. Moreover, ST-segment depression as the unique find is the least frequent ECG abnormality on TTC, and is very uncommon compared with ACS<sup>[18]</sup>.

#### **Evolution of the ECG abnormalities**

The repolarization changes follow a pattern very similar to STEMI, but the normalization of ST-segment and the appearance of T waves inversion usually occur more rapidly in TTC. Therefore, one can not rule out that patients presenting with T waves inversion in the first ECG, have previously had a short unnoticed phase with ST-segment elevation. In general, the evolution of the main ECG abnormalities described in TTC patients is, in order: ST-segment elevation, development of negative T waves while ST-segment is normalizing, and prolongation of QT-interval. The time to resolve both T waves inversion and prolonged QT-interval is highly variable, it could

be take few weeks or several months<sup>[67]</sup>. Interestingly, the ECG abnormalities take more time to resolve than the wall motion impairment. Other electrocardiographic abnormalities have been described, including a high prevalence of low QRS voltage and attenuation of the amplitude of QRS complexes, which might help to support the suspicion of TTC<sup>[68]</sup>.

#### **QT-interval**

Although a prolonged QT-interval is very common (47.7% by Templin *et al.*<sup>[18]</sup>; 78.8% by Núñez *et al.*<sup>[14]</sup>), the incidence of ventricular arrhythmias is very low, which highlight a benign prognosis of this form of acquired long QT-interval. Interestingly, Gopalakrishnan *et al.*<sup>[69]</sup> found a strong correlation between prolonged-QTc interval at presentation and overall outcome.

#### **Q-waves**

Given the full recovery of myocardial damage, it is ex-

**Table 4** Electrocardiographic findings in takotsubo cardiomyopathy

T waves inversion	ST-segment	QRS complex	Q waves
Are the most frequent finding along ECG evolution	Makes priority rule out obstructive coronary artery disease	aVR lead is especially sensible to changes in voltage because it "faces" the apex	Permanent pathological Q waves are exceptional
Appear mainly in precordial leads (V2-V6)	More frequent on precordial leads, except V1		
Negative T waves are deep, symmetrical and widespread	Reciprocal depression is less frequent than in STEMI		
Progressive QT-interval prolongation	Suspicious combinations: ST-depression in aVR plus no elevation in V1 (91% sensitivity, 96% specificity) <sup>[87]</sup> The sum of elevation in V4-V6/V1-V3 $\geq$ 1 (77% sensitivity, 80% specificity) <sup>[65]</sup>		
No negative T wave in V1 plus positive T wave in aVR must raise suspicion (95% sensitivity, 97% specificity) <sup>[62]</sup>	Level of ST segment elevation lesser than in anterior STEMI		

ECG: Electrocardiogram; STEMI: ST-segment elevation myocardial infarction.

ceptional to find permanent pathological Q waves on previously normal hearts in patients with TTC<sup>[70]</sup>.

The similarities between TTC and anterior-STEMI have aroused a great interest on scientific community in searching of electrocardiographic features that help to distinguish them from the onset<sup>[65,66,71,72]</sup>. Although some ECG signs have been described in patients with TTC (Table 4), more studies are needed, particularly prospective, rigorously comparing the electrocardiographic findings with anterior-STEMI<sup>[9]</sup>. Currently, there are no ECG signs which alone may rule out a culprit coronary artery stenosis<sup>[73]</sup>. Figure 2 shows an example of the most common ECG findings in TTC patients.

### Arrhythmias

Incidence and type of arrhythmias observed in different TTC series varies widely, but it has in common that usually resolve after overcoming the acute setting. In our registry, paroxysmal atrial fibrillation is the more common sustained tachyarrhythmia (11%). Sinus bradycardia and different degrees of atrioventricular block have been observed. Ventricular arrhythmias such as ventricular tachycardia (4.8%) and ventricular fibrillation (VF) (0.7%) are uncommon in the acute phase in our experience<sup>[14]</sup>, which is concordant with other observational studies<sup>[18]</sup>. Torsades de pointes have rarely been reported. However, among patients with TTC who present prolonged QT-interval, male sex has been associated with more risk of Torsades de pointes, as well as severe left ventricular systolic dysfunction, bradycardia, hypokalemia and use of QT-prolonging agents<sup>[74]</sup>. Some patients debut with sudden death due to VF<sup>[75,76]</sup>, although in these cases it is unclear if VF is a trigger or consequence of TTC<sup>[77]</sup>.

## TREATMENT

Because pathophysiologic mechanisms are not clear yet, there is no consensus on specific treatment to this condition. In fact, treatment consists mainly on treatment of heart failure and its complications. Based on the theory

of high catecholamine levels, use of beta-blockers seems reasonable, but caution must be taken due to the high frequency of heart failure on these patients<sup>[78]</sup>. However, it is striking that in some case series a significant percent of patients were on treatment with beta-blockers at the time of debut. Furthermore, in patients with recurrences, there are no differences regarding incidence among those who were being treated with beta-blockers and those without. Beta-blockers do not appear to have a protective effect for this syndrome based on these results<sup>[18,79]</sup>.

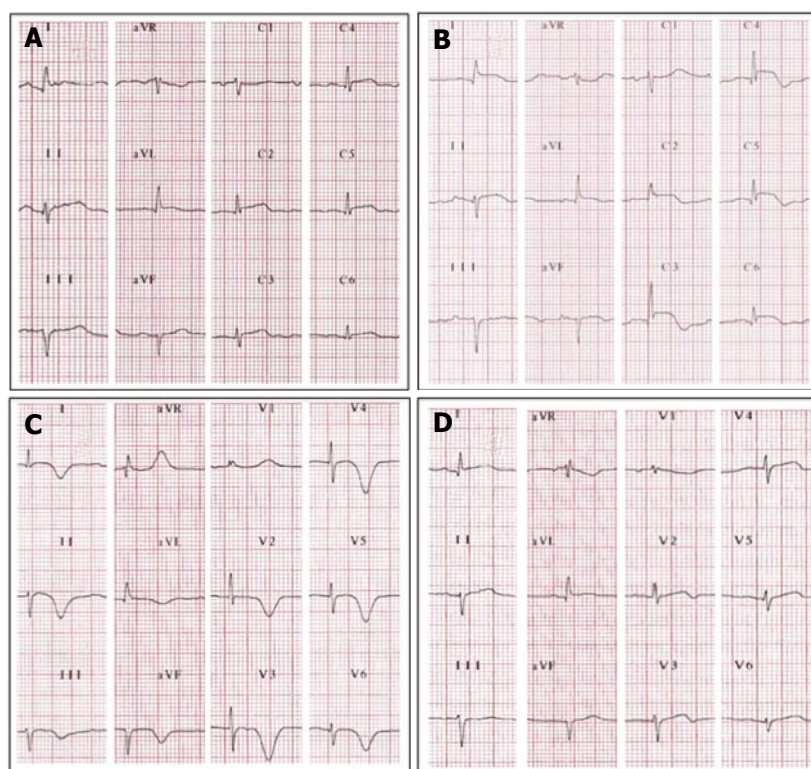
Anticoagulation is indicated to the management of ventricular thrombus and should be maintained at least until confirm its resolution. It must be considered an early anticoagulation therapy irrespective of the presence of ventricular thrombus at admission, specially in patients with high risk of thromboembolic events<sup>[9,80]</sup>.

Patients with hemodynamic instability may require positive inotropic drugs and circulatory support devices such as intra-aortic balloon pump counterpulsation or extracorporeal life support in case of refractory cardiogenic shock. However, it is not clear the benefit of exogenous catecholamines taking into account the pathophysiology of this syndrome, so positive inotropic drugs should be used with caution with the minimum dose required to maintaining an acceptable hemodynamic status<sup>[78,81]</sup>.

Echocardiography is very useful to guide the treatment in patients with TTC. In presence of DLVOTO, SAM and hemodynamic instability, beta-blockers and/or intravenous fluids are preferred (in absence of significant pulmonary congestion) instead of positive inotropic drugs<sup>[9,82-84]</sup>.

Typically, TTC patients are initially treated with the standard of care for ACS at the moment of presenting to the emergency department, due to the similarities among these two diseases. This decision implies that TTC patients must receive dual antiplatelet and anticoagulation therapy until coronary angiography is





**Figure 2** Electrocardiographic evolutionary changes in a 65-year-old woman with typical takotsubo cardiomyopathy. A: Initial electrocardiographic (ECG) after 3 h of symptoms. There is diffuse ST-segment elevation (DI, aVL and all precordial leads except on V1); B: ECG after 24 h of symptoms. The ST-segment elevation seems to be more prominent. Note ST-segment depression on aVR. The T waves start to invert on leads with ST-segment elevation, except on V1 where there is a more prominent positive T wave; C: Third day. The ST-segment is almost normal. The T waves are now inverted, deep, wide and symmetrical on all leads except on aVR and V1 where they are positive. The corrected QT-interval is prolonged (520 milliseconds); D: ECG 3 wk later, outpatient. The T waves are almost normal and the QT-interval is not prolonged.

performed and culprit coronary obstructive disease is discarded.

Finally, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers have been associated with better survival<sup>[18]</sup>.

## PROGNOSIS

By definition, TTC left ventricular dysfunction is completely reversible. The involvement of the right ventricle is occasional. Serious complications and recurrences are infrequent. So, TTC has been traditionally considered as a benign cardiac syndrome in absence of significant comorbid conditions<sup>[79,85,86]</sup>. However, this syndrome significantly contributes to morbidity and mortality. Some recent large observational studies have shown that TTC has a poorer prognosis than it was believed, comparable with ACS<sup>[7,18]</sup>, and related to the patient's risk profile such as frailty and associated comorbidities. Templin *et al.*<sup>[18]</sup> found that elderly patients with emotional triggers have a low risk of significant cardiovascular events, while younger patients with physical triggers and acute neurologic or psychiatric diseases have an increased risk of acute complications. The risk of mortality seems to be higher in men and patients with underlying critical illness<sup>[8]</sup>.

The recurrence of TTC is low; Elesber *et al.*<sup>[79]</sup> have

reported an average yearly recurrence rate of 2.9% in the first few years, decreasing later to 1.3% per year, which is similar to the recurrence rate reported by Templin *et al.*<sup>[18]</sup> (1.8% per patient-year).

## CONCLUSION

TTC is a wide spectrum syndrome that clinically mimics an ACS in absence of significant epicardial coronary artery disease to explain the extent of the wall motion abnormalities. Nowadays, there have not been clearly identified electrocardiographic signs to reliably differentiate TTC from ACS in the acute phase. Therefore, knowledge of the coronary anatomy is mandatory. The pathophysiological mechanism is not well understood, but it seems that an intense release of catecholamines triggers myocardial stunning. In the midway, CMD and abnormalities on myocardium metabolism have been highlighted as potential involved mechanisms. Treatment in the acute phase should be directed to treat complications, including heart failure, arrhythmias and ventricular thrombus, while long-term medical therapy remains empirical due to limited available data. Although it was thought that prognosis is good, it seems increasingly evident that TTC patients may have poorer outcomes, even similar with patients with ACS. Angiotensin-converting-enzyme inhibitors and angiotensin-receptor

blockers have been associated with improved survival. We need more rigorous prospective studies to continue on the way of understanding this enigmatic disease.

## REFERENCES

- 1 **Dote K**, Sato H, Tateishi H, Uchida T, Ishihara M. [Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases]. *J Cardiol* 1991; **21**: 203-214 [PMID: 1841907]
- 2 **Maron BJ**, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006; **113**: 1807-1816 [PMID: 16567565 DOI: 10.1161/CIRCULATIONAHA.106.174287]
- 3 **Sharkey SW**, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, Haas TS, Hodges JS, Maron BJ. Natural history and expansive clinical profile of stress (takotsubo) cardiomyopathy. *J Am Coll Cardiol* 2010; **55**: 333-341 [PMID: 20117439 DOI: 10.1016/j.jacc.2009.08.057]
- 4 **Sharkey SW**, Lesser JR, Maron MS, Maron BJ. Why not just call it takotsubo cardiomyopathy: a discussion of nomenclature. *J Am Coll Cardiol* 2011; **57**: 1496-1497 [PMID: 21435521 DOI: 10.1016/j.jacc.2010.11.029]
- 5 **Niccoli G**, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J* 2015; **36**: 475-481 [PMID: 25526726 DOI: 10.1093/eurheartj/ehu469]
- 6 **Minhas AS**, Hughey AB, Kolias TJ. Nationwide Trends in Reported Incidence of Takotsubo Cardiomyopathy from 2006 to 2012. *Am J Cardiol* 2015; **116**: 1128-1131 [PMID: 26279109 DOI: 10.1016/j.amjcard.2015.06.042]
- 7 **Redfors B**, Vedar R, Ångerås O, Råmunddal T, Petursson P, Haraldsson I, Ali A, Dworeck C, Odenstedt J, Ioaness D, Libungan B, Shao Y, Albertsson P, Stone GW, Omerovic E. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction - A report from the SWEDEHEART registry. *Int J Cardiol* 2015; **185**: 282-289 [PMID: 25818540 DOI: 10.1016/j.ijcard.2015.03.162]
- 8 **Khera R**, Light-McGroarty K, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for takotsubo cardiomyopathy in the United States. *Am Heart J* 2016; **172**: 53-63 [PMID: 26856216 DOI: 10.1016/j.ahj.2015.10.022]
- 9 **Lyon AR**, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016; **18**: 8-27 [PMID: 26548803 DOI: 10.1002/ejhf.424]
- 10 **Akashi YJ**, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. *Nat Rev Cardiol* 2015; **12**: 387-397 [PMID: 25855605 DOI: 10.1038/nrcardio.2015.39]
- 11 **Parodi G**, Del Pace S, Carrabba N, Salvadori C, Memisha G, Simonetti I, Antoniucci D, Gensini GF. Incidence, clinical findings, and outcome of women with left ventricular apical ballooning syndrome. *Am J Cardiol* 2007; **99**: 182-185 [PMID: 17223415 DOI: 10.1016/j.amjcard.2006.07.080]
- 12 **Madias JE**. Low prevalence of diabetes mellitus in patients with Takotsubo syndrome: A plausible 'protective' effect with pathophysiologic connotations. *Eur Heart J Acute Cardiovasc Care* 2016; **5**: 164-170 [PMID: 25673782 DOI: 10.1177/2048872615570761]
- 13 **Kurowski V**, Kaiser A, von Hof K, Killermann DP, Mayer B, Hartmann F, Schunkert H, Radke PW. Apical and midventricular transient left ventricular dysfunction syndrome (takotsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest* 2007; **132**: 809-816 [PMID: 17573507 DOI: 10.1378/chest.07-0608]
- 14 **Núñez Gil IJ**, Andrés M, Almendro Delia M, Sionis A, Martín A, Bastante T, Córdoba Soriano JG, Linares Vicente JA, González Sucarrats S, Sánchez-Grande Flecha A. Characterization of Takotsubo Cardiomyopathy in Spain: Results from the RETAKO National Registry. *Rev Esp Cardiol (Engl Ed)* 2015; **68**: 505-512 [PMID: 25544669 DOI: 10.1016/j.rec.2014.07.026]
- 15 **Tsuchihashi K**, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, Yoshiyama M, Miyazaki S, Haze K, Ogawa H, Honda T, Hase M, Kai R, Morii I. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. *J Am Coll Cardiol* 2001; **38**: 11-18 [PMID: 11451258 DOI: 10.1016/S0735-1097(01)01316-X]
- 16 **Eshtehardi P**, Koestner SC, Adorjan P, Windecker S, Meier B, Hess OM, Wahl A, Cook S. Transient apical ballooning syndrome-clinical characteristics, ballooning pattern, and long-term follow-up in a Swiss population. *Int J Cardiol* 2009; **135**: 370-375 [PMID: 18599137 DOI: 10.1016/j.ijcard.2008.03.088]
- 17 **Ahmed S**, Ungprasert P, Ratanapo S, Hussain T, Riesenfeld EP. Clinical characteristics of takotsubo cardiomyopathy in north america. *N Am J Med Sci* 2013; **5**: 77-81 [PMID: 23641366 DOI: 10.4103/1947-2714.107520]
- 18 **Templin C**, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med* 2015; **373**: 929-938 [PMID: 26332547 DOI: 10.1056/NEJMoa1406761]
- 19 **Summers MR**, Lennon RJ, Prasad A. Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (takotsubo/stress-induced cardiomyopathy): potential pre-disposing factors? *J Am Coll Cardiol* 2010; **55**: 700-701 [PMID: 20170799 DOI: 10.1016/j.jacc.2009.10.031]
- 20 **Sanchez-Recalde A**, Costero O, Oliver JM, Iborra C, Ruiz E, Sobrino JA. Images in cardiovascular medicine. Pheochromocytoma-related cardiomyopathy: inverted Takotsubo contractile pattern. *Circulation* 2006; **113**: e738-e739 [PMID: 16651478 DOI: 10.1161/CIRCULATIONAHA.105.581108]
- 21 **Naderi N**, Amin A, Setayesh A, Pouraliakbar H, Mozaffari K, Maleki M. Pheochromocytoma-induced reverse takotsubo with rapid recovery of left ventricular function. *Cardiol J* 2012; **19**: 527-531 [PMID: 23042320 DOI: 10.5603/CJ.2012.0097]
- 22 **Kimura S**, Mitsuma W, Ito M, Suzuki H, Hosaka Y, Hirayama S, Hanyu O, Hirano S, Kodama M, Aizawa Y. Inverted Takotsubo contractile pattern caused by pheochromocytoma with tall upright T-waves, but not typical deep T-wave inversion. *Int J Cardiol* 2010; **139**: e15-e17 [PMID: 18722026 DOI: 10.1016/j.ijcard.2008.06.073]
- 23 **Wittstein IS**, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; **352**: 539-548 [PMID: 15703419 DOI: 10.1056/NEJMoa043046]
- 24 **Madias JE**. Coronary vasospasm is an unlikely cause of Takotsubo syndrome, although we should keep an open mind. *Int J Cardiol* 2014; **176**: 1-5 [PMID: 25043215 DOI: 10.1016/j.ijcard.2014.06.069]
- 25 **Kurisu S**, Sato H, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, Kono Y, Umemura T, Nakamura S. Tako-tsubo-like left ventricular

- dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* 2002; **143**: 448-455 [PMID: 11868050 DOI: 10.1067/mhj.2002.120403]
- 26 **Ibáñez B**, Navarro F, Farré J, Marcos-Alberca P, Orejas M, Rábago R, Rey M, Romero J, Iñiguez A, Córdoba M. [Takotsubo syndrome associated with a long course of the left anterior descending coronary artery along the apical diaphragmatic surface of the left ventricle]. *Rev Esp Cardiol* 2004; **57**: 209-216 [PMID: 15056424 DOI: 10.1016/S0300-8932(04)77092-X]
  - 27 **Alfonso F**, Núñez-Gil IJ, Hernández R. Optical coherence tomography findings in Tako-Tsubo cardiomyopathy. *Circulation* 2012; **126**: 1663-1664 [PMID: 23008472 DOI: 10.1161/CIRCULATIONAHA.112.122200]
  - 28 **Bybee KA**, Murphy J, Prasad A, Wright RS, Lerman A, Rihal CS, Chareonthaitawee P. Acute impairment of regional myocardial glucose uptake in the apical ballooning (takotsubo) syndrome. *J Nucl Cardiol* 2006; **13**: 244-250 [PMID: 16580961 DOI: 10.1016/j.nuclcard.2006.01.016]
  - 29 **Yoshida T**, Hibino T, Kako N, Murai S, Oguri M, Kato K, Yajima K, Ohte N, Yokoi K, Kimura G. A pathophysiologic study of takotsubo cardiomyopathy with F-18 fluorodeoxyglucose positron emission tomography. *Eur Heart J* 2007; **28**: 2598-2604 [PMID: 17921529 DOI: 10.1093/eurheartj/ehm401]
  - 30 **Ito K**, Sugihara H, Kinoshita N, Azuma A, Matsubara H. Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using 99mTc-tetrofosmin, 123I-BMIPP, 123I-MIBG and 99mTc-PYP myocardial SPECT. *Ann Nucl Med* 2005; **19**: 435-445 [PMID: 16248379 DOI: 10.1007/BF02985570]
  - 31 **Matsuo S**, Nakajima K, Kinuya S, Yamagishi M. Diagnostic utility of 123I-BMIPP imaging in patients with Takotsubo cardiomyopathy. *J Cardiol* 2014; **64**: 49-56 [PMID: 24331764 DOI: 10.1016/j.jjcc.2013.10.019]
  - 32 **Kume T**, Akasaka T, Kawamoto T, Yoshitani H, Watanabe N, Neishi Y, Wada N, Yoshida K. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. *Circ J* 2005; **69**: 934-939 [PMID: 16041162 DOI: 10.1253/circj.69.934]
  - 33 **Meimoun P**, Malaquin D, Benali T, Boulanger J, Zemir H, Tribouilloy C. Transient impairment of coronary flow reserve in tako-tsubo cardiomyopathy is related to left ventricular systolic parameters. *Eur J Echocardiogr* 2009; **10**: 265-270 [PMID: 18755700 DOI: 10.1093/ejehocard/jen222]
  - 34 **Kurusu S**, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, Umemura T, Nakamura S, Yoshida M, Sato H. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. *J Am Coll Cardiol* 2003; **41**: 743-748 [PMID: 12628716 DOI: 10.1016/S0735-1097(02)02924-8]
  - 35 **Bybee KA**, Prasad A, Barsness GW, Lerman A, Jaffe AS, Murphy JG, Wright RS, Rihal CS. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. *Am J Cardiol* 2004; **94**: 343-346 [PMID: 15276100 DOI: 10.1016/j.amjcard.2004.04.030]
  - 36 **Elesber A**, Lerman A, Bybee KA, Murphy JG, Barsness G, Singh M, Rihal CS, Prasad A. Myocardial perfusion in apical ballooning syndrome correlate of myocardial injury. *Am Heart J* 2006; **152**: 469.e9-469.13 [PMID: 16923415 DOI: 10.1016/j.ahj.2006.06.007]
  - 37 **d'Avenia M**, Citro R, De Marco M, Veronese A, Rosati A, Visone R, Leptidis S, Philippen L, Vitale G, Cavallo A, Silverio A, Protta C, Gravina P, De Cola A, Carletti E, Coppola G, Gallo S, Provenza G, Bossone E, Piscione F, Hahne M, De Windt LJ, Turco MC, De Laurenzi V. A novel miR-371a-5p-mediated pathway, leading to BAG3 upregulation in cardiomyocytes in response to epinephrine, is lost in Takotsubo cardiomyopathy. *Cell Death Dis* 2015; **6**: e1948 [PMID: 26512958 DOI: 10.1038/cddis.2015.280]
  - 38 **Lyon AR**, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy--a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med* 2008; **5**: 22-29 [PMID: 18094670 DOI: 10.1038/npcardio1066]
  - 39 **Tranter MH**, Wright PT, Sikkil MB, Lyon AR. Takotsubo cardiomyopathy: the pathophysiology. *Heart Fail Clin* 2013; **9**: 187-96, viii-ix [PMID: 23562119 DOI: 10.1016/j.hfc.2012.12.010]
  - 40 **Hurst RT**, Askew JW, Reuss CS, Lee RW, Sweeney JP, Fortuin FD, Oh JK, Tajik AJ. Transient midventricular ballooning syndrome: a new variant. *J Am Coll Cardiol* 2006; **48**: 579-583 [PMID: 16875987 DOI: 10.1016/j.jacc.2006.06.015]
  - 41 **Manzanal A**, Ruiz L, Madrazo J, Makan M, Perez J. Inverted Takotsubo cardiomyopathy and the fundamental diagnostic role of echocardiography. *Tex Heart Inst J* 2013; **40**: 56-59 [PMID: 23467068]
  - 42 **Angelini P**, Monge J, Simpson L. Biventricular takotsubo cardiomyopathy: case report and general discussion. *Tex Heart Inst J* 2013; **40**: 312-315 [PMID: 23914029]
  - 43 **Daoko J**, Rajachandran M, Savarese R, Orme J. Biventricular takotsubo cardiomyopathy: case study and review of literature. *Tex Heart Inst J* 2013; **40**: 305-311 [PMID: 23914028]
  - 44 **Koo N**, Yoon BW, Song Y, Lee CK, Lee TY, Hong JY. Biventricular Takotsubo Cardiomyopathy Associated with Epilepsy. *J Cardiovasc Ultrasound* 2015; **23**: 262-265 [PMID: 26755936 DOI: 10.4250/jcu.2015.23.4.262]
  - 45 **Stähli BE**, Ruschitzka F, Enseleit F. Isolated right ventricular ballooning syndrome: a new variant of transient cardiomyopathy. *Eur Heart J* 2011; **32**: 1821 [PMID: 21444364 DOI: 10.1093/eurheartj/ehr079]
  - 46 **Burgdorf C**, Hunold P, Radke PW, Schunkert H, Kurowski V. Isolated right ventricular stress-induced ("Tako-Tsubo") cardiomyopathy. *Clin Res Cardiol* 2011; **100**: 617-619 [PMID: 21318558 DOI: 10.1007/s00392-011-0293-4]
  - 47 **Ehl NF**, Zurek M, Rickli H, Maeder MT. "Double takotsubo": first description of the sequence of classical followed by inverted type in a young woman. *Int J Cardiol* 2014; **174**: e36-e37 [PMID: 24780539 DOI: 10.1016/j.ijcard.2014.04.064]
  - 48 **Eitel I**, Lücke C, Behrendt F, Sareban M, Gutberlet M, Schuler G, Thiele H. Full recovery of Takotsubo cardiomyopathy (apical ballooning) in two days. *Int J Cardiol* 2010; **143**: e51-e53 [PMID: 19157601 DOI: 10.1016/j.ijcard.2008.12.044]
  - 49 **Shimokawahara H**, Sonoda M, Tanaka H, Kashima K, Nagayoshi S, Kawasaki D, Ikeda D, Nagano S, Tanaka Y, Nakamura K. Case of transient mid-ventricular ballooning syndrome with a rapid and uncommon recovery. *J Cardiol* 2009; **54**: 311-316 [PMID: 19782272 DOI: 10.1016/j.jjcc.2008.12.004]
  - 50 **Citro R**, Piscione F, Parodi G, Salerno-Uriarte J, Bossone E. Role of echocardiography in takotsubo cardiomyopathy. *Heart Fail Clin* 2013; **9**: 157-66, viii [PMID: 23562116 DOI: 10.1016/j.hfc.2012.12.014]
  - 51 **Citro R**, Lyon AR, Meimoun P, Omerovic E, Redfors B, Buck T, Lerakis S, Parodi G, Silverio A, Eitel I, Schneider B, Prasad A, Bossone E. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: clinical and prognostic implications. *J Am Soc Echocardiogr* 2015; **28**: 57-74 [PMID: 25282664 DOI: 10.1016/j.echo.2014.08.020]
  - 52 **Eitel I**, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, Francione M, Desch S, Gutberlet M, Stroh O, Schuler G, Schulz-Menger J, Thiele H, Friedrich MG. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011; **306**: 277-286 [PMID: 21771988 DOI: 10.1001/jama.2011.992]
  - 53 **Abdel-Aty H**, Cocker M, Friedrich MG. Myocardial edema is a feature of Tako-Tsubo cardiomyopathy and is related to the severity of systolic dysfunction: insights from T2-weighted cardiovascular magnetic resonance. *Int J Cardiol* 2009; **132**: 291-293 [PMID: 18086501 DOI: 10.1016/j.ijcard.2007.08.102]
  - 54 **Joshi SB**, Chao T, Herzka DA, Zeman PR, Cooper HA, Lindsay J, Fuisz AR. Cardiovascular magnetic resonance T2 signal abnormalities in left ventricular ballooning syndrome. *Int J Cardiovasc Imaging* 2010; **26**: 227-232 [PMID: 19862639 DOI: 10.1007/s10554-009-9515-5]
  - 55 **Tada H**. Unraveling the riddle of transient T-wave inversion (Wellens' ECG pattern): T2-weighted magnetic resonance imaging identifies myocardial edema. *Heart Rhythm* 2011; **8**: 1635-1636



- [PMID: 21699853 DOI: 10.1016/j.hrthm.2011.05.013]
- 56 **Migliore F**, Zorzi A, Marra MP, Basso C, Corbetti F, De Lazzari M, Tarantini G, Buja P, Lacognata C, Thiene G, Corrado D, Iliceto S. Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction. *Heart Rhythm* 2011; **8**: 1629-1634 [PMID: 21699846 DOI: 10.1016/j.hrthm.2011.04.035]
  - 57 **Dastidar AG**, Frontera A, Palazzuoli A, Bucciarelli-Ducci C. TakoTsubo cardiomyopathy: unravelling the malignant consequences of a benign disease with cardiac magnetic resonance. *Heart Fail Rev* 2015; **20**: 415-421 [PMID: 25896529 DOI: 10.1007/s10741-015-9489-4]
  - 58 **Ahtarovski KA**, Iversen KK, Christensen TE, Andersson H, Grande P, Holmvang L, Bang L, Hasbak P, Lønborg JT, Madsen PL, Engstrøm T, Vejlsø NG. Takotsubo cardiomyopathy, a two-stage recovery of left ventricular systolic and diastolic function as determined by cardiac magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging* 2014; **15**: 855-862 [PMID: 24525137 DOI: 10.1093/ehjci/jeu004]
  - 59 **Testa M**, Feola M. Usefulness of myocardial positron emission tomography/nuclear imaging in Takotsubo cardiomyopathy. *World J Radiol* 2014; **6**: 502-506 [PMID: 25071891 DOI: 10.4329/wjr.v6.i7.502]
  - 60 **Mena LM**, Martín F, Melero A, Ramos A, Jiménez IR. [Takotsubo syndrome. Usefulness of nuclear medicine studies]. *Rev Esp Med Nucl* 2011; **30**: 104-106 [PMID: 21334776 DOI: 10.1016/j.remna.2010.09.009]
  - 61 **Feola M**, Chauvie S, Rosso GL, Biggi A, Ribichini F, Bobbio M. Reversible impairment of coronary flow reserve in takotsubo cardiomyopathy: a myocardial PET study. *J Nucl Cardiol* 2008; **15**: 811-817 [PMID: 18984457 DOI: 10.1016/j.nucard.2008.06.010]
  - 62 **Kosuge M**, Ebina T, Hibi K, Tsukahara K, Iwahashi N, Gohbara M, Matsuzawa Y, Okada K, Morita S, Umemura S, Kimura K. Differences in negative T waves among acute coronary syndrome, acute pulmonary embolism, and Takotsubo cardiomyopathy. *Eur Heart J Acute Cardiovasc Care* 2012; **1**: 349-357 [PMID: 24062927 DOI: 10.1177/2048872612466790]
  - 63 **Song BG**, Chun WJ, Park YH, Kang GH, Oh J, Lee SC, Park SW, Oh JK. The clinical characteristics, laboratory parameters, electrocardiographic, and echocardiographic findings of reverse or inverted takotsubo cardiomyopathy: comparison with mid or apical variant. *Clin Cardiol* 2011; **34**: 693-699 [PMID: 22031226 DOI: 10.1002/clc.20953]
  - 64 **Núñez-Gil IJ**, Luaces M, Garcia-Rubira JC, Zamorano J. Electrocardiographic criteria in Takotsubo cardiomyopathy and race differences: Asians versus Caucasians. *J Am Coll Cardiol* 2010; **56**: 1433-1444; author reply 1434 [PMID: 20947004 DOI: 10.1016/j.jacc.2010.06.025]
  - 65 **Ogura R**, Hiasa Y, Takahashi T, Yamaguchi K, Fujiwara K, Ohara Y, Nada T, Ogata T, Kusunoki K, Yuba K, Hosokawa S, Kishi K, Ohtani R. Specific findings of the standard 12-lead ECG in patients with 'Takotsubo' cardiomyopathy: comparison with the findings of acute anterior myocardial infarction. *Circ J* 2003; **67**: 687-690 [PMID: 12890911 DOI: 10.1253/circj.67.687]
  - 66 **Jim MH**, Chan AO, Tsui PT, Lau ST, Siu CW, Chow WH, Lau CP. A new ECG criterion to identify takotsubo cardiomyopathy from anterior myocardial infarction: role of inferior leads. *Heart Vessels* 2009; **24**: 124-130 [PMID: 19337796 DOI: 10.1007/s00380-008-1099-9]
  - 67 **Kurisu S**, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nakamura S, Yoshida M, Mitsuba N, Hata T, Sato H. Time course of electrocardiographic changes in patients with tako-tsubo syndrome: comparison with acute myocardial infarction with minimal enzymatic release. *Circ J* 2004; **68**: 77-81 [PMID: 14695470 DOI: 10.1253/circj.68.77]
  - 68 **Madias JE**. Transient attenuation of the amplitude of the QRS complexes in the diagnosis of Takotsubo syndrome. *Eur Heart J Acute Cardiovasc Care* 2014; **3**: 28-36 [PMID: 24562801 DOI: 10.1177/2048872613504311]
  - 69 **Gopalakrishnan M**, Hassan A, Villines D, Nasr S, Chandrasekaran M, Klein LW. Predictors of short- and long-term outcomes of Takotsubo cardiomyopathy. *Am J Cardiol* 2015; **116**: 1586-1590 [PMID: 26431577 DOI: 10.1016/j.amjcard.2015.08.024]
  - 70 **Looi JL**, Wong CW, Lee M, Khan A, Webster M, Kerr AJ. Usefulness of ECG to differentiate Takotsubo cardiomyopathy from acute coronary syndrome. *Int J Cardiol* 2015; **199**: 132-140 [PMID: 26188834 DOI: 10.1016/j.ijcard.2015.07.046]
  - 71 **Inoue M**, Shimizu M, Ino H, Yamaguchi M, Terai H, Fujino N, Sakata K, Funada A, Tatami R, Ishise S, Kanaya H, Mabuchi H. Differentiation between patients with takotsubo cardiomyopathy and those with anterior acute myocardial infarction. *Circ J* 2005; **69**: 89-94 [PMID: 15635210 DOI: 10.1253/circj.69.89]
  - 72 **Kosuge M**, Kimura K. Electrocardiographic findings of takotsubo cardiomyopathy as compared with those of anterior acute myocardial infarction. *J Electrocardiol* 2014; **47**: 684-689 [PMID: 24735641 DOI: 10.1016/j.jelectrocard.2014.03.004]
  - 73 **Vervaat FE**, Christensen TE, Smeijers L, Holmvang L, Hasbak P, Szabó BM, Widdershoven JW, Wagner GS, Bang LE, Gorgels AP. Is it possible to differentiate between Takotsubo cardiomyopathy and acute anterior ST-elevation myocardial infarction? *J Electrocardiol* 2015; **48**: 512-519 [PMID: 25818746 DOI: 10.1016/j.jelectrocard.2015.02.008]
  - 74 **Samuelov-Kinori L**, Kinori M, Kogan Y, Swartzon M, Shalev H, Guy D, Ferenidou F, Mashav N, Sadeh B, Atzmony L, Kliuk-Ben-Basat O, Steinvil A, Justo D. Takotsubo cardiomyopathy and QT interval prolongation: who are the patients at risk for torsades de pointes? *J Electrocardiol* 2009; **42**: 353-357.e1 [PMID: 19261294 DOI: 10.1016/j.jelectrocard.2009.01.005]
  - 75 **Gasparetto N**, Zorzi A, Perazzolo Marra M, Migliore F, Napodano M, Corrado D, Iliceto S, Cacciavillani L. Atypical (mid-ventricular) Takotsubo syndrome in a survival of out-of-hospital ventricular fibrillation: cause or consequence? *Int J Cardiol* 2014; **172**: e51-e53 [PMID: 24486060 DOI: 10.1016/j.ijcard.2013.12.064]
  - 76 **Liang JJ**, Cha YM, Oh JK, Prasad A. Sudden cardiac death: an increasingly recognized presentation of apical ballooning syndrome (Takotsubo cardiomyopathy). *Heart Lung* 2013; **42**: 270-272 [PMID: 23702320 DOI: 10.1016/j.hrtlung.2013.04.003]
  - 77 **Madias JE**. Ventricular fibrillation and Takotsubo syndrome: which one was first? *Int J Cardiol* 2014; **173**: 506 [PMID: 24708932 DOI: 10.1016/j.ijcard.2014.03.143]
  - 78 **Madhavan M**, Rihal CS, Lerman A, Prasad A. Acute heart failure in apical ballooning syndrome (TakoTsubo/stress cardiomyopathy): clinical correlates and Mayo Clinic risk score. *J Am Coll Cardiol* 2011; **57**: 1400-1401 [PMID: 21414539 DOI: 10.1016/j.jacc.2010.10.038]
  - 79 **Elesber AA**, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four-year recurrence rate and prognosis of the apical ballooning syndrome. *J Am Coll Cardiol* 2007; **50**: 448-452 [PMID: 17662398 DOI: 10.1016/j.jacc.2007.03.050]
  - 80 **de Gregorio C**. Cardioembolic outcomes in stress-related cardiomyopathy complicated by ventricular thrombus: a systematic review of 26 clinical studies. *Int J Cardiol* 2010; **141**: 11-17 [PMID: 19913310 DOI: 10.1016/j.ijcard.2009.09.468]
  - 81 **Angue M**, Soubirou L, Vandroux D, Cordier C, Martinet O, Gauzere BA, Braunberger E. Beneficial effects of intravenous beta-blockers in Tako-Tsubo syndrome with dynamic left ventricular outflow tract obstruction and severe haemodynamic impairment. *Int J Cardiol* 2014; **177**: e56-e57 [PMID: 25449492 DOI: 10.1016/j.ijcard.2014.09.162]
  - 82 **Bonacchi M**, Maiani M, Harmelin G, Sani G. Intractable cardiogenic shock in stress cardiomyopathy with left ventricular outflow tract obstruction: is extra-corporeal life support the best treatment? *Eur J Heart Fail* 2009; **11**: 721-727 [PMID: 19468019 DOI: 10.1093/eurjhf/hfp068]
  - 83 **Shah BN**, Curzen NP. Dynamic left ventricular outflow tract obstruction and acute heart failure in tako-tsubo cardiomyopathy. *J Am Coll Cardiol* 2011; **58**: 1195-1196; author reply 1196 [PMID: 21884964 DOI: 10.1016/j.jacc.2011.03.062]
  - 84 **Migliore F**, Bilato C, Isabella G, Iliceto S, Tarantini G. Haemodynamic effects of acute intravenous metoprolol in apical



- ballooning syndrome with dynamic left ventricular outflow tract obstruction. *Eur J Heart Fail* 2010; **12**: 305-308 [PMID: 20097684 DOI: 10.1093/eurjhf/hfp205]
- 85 **Sharkey SW**, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, Maron BJ. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005; **111**: 472-479 [PMID: 15687136 DOI: 10.1161/01.CIR.0000153801.51470.EB]
- 86 **Prasad A**. Apical ballooning syndrome: an important differential diagnosis of acute myocardial infarction. *Circulation* 2007; **115**: e56-e59 [PMID: 17283269 DOI: 10.1161/CIRCULATIONAHA.106.669341]
- 87 **Kosuge M**, Ebina T, Hibi K, Morita S, Okuda J, Iwahashi N, Tsukahara K, Nakachi T, Kiyokuni M, Ishikawa T, Umemura S, Kimura K. Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. *J Am Coll Cardiol* 2010; **55**: 2514-2516 [PMID: 20510222 DOI: 10.1016/j.jacc.2009.12.059]

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## Retrospective Cohort Study

# Impact of clinical and procedural factors upon C reactive protein dynamics following transcatheter aortic valve implantation

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## Abstract

**AIM:** To determine the effect of procedural and clinical factors upon C reactive protein (CRP) dynamics following transcatheter aortic valve implantation (TAVI).

**METHODS:** Two hundred and eight consecutive patients that underwent transfemoral TAVI at two hospitals (Imperial, College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom and San Raffaele Scientific Institute, Milan, Italy) were included. Daily venous plasma CRP levels were measured for up to 7 d following the procedure (or up to discharge). Procedural factors and 30-d safety outcomes according to

the Valve Academic Research Consortium 2 definition were collected.

**RESULTS:** Following TAVI, CRP significantly increased reaching a peak on day 3 of  $87.6 \pm 5.5$  mg/dL,  $P < 0.001$ . Patients who developed clinical signs and symptoms of sepsis had significantly increased levels of CRP ( $P < 0.001$ ). The presence of diabetes mellitus was associated with a significantly higher peak CRP level at day 3 ( $78.4 \pm 3.2$  vs  $92.2 \pm 4.4$ ,  $P < 0.001$ ). There was no difference in peak CRP release following balloon-expandable or self-expandable TAVI implantation ( $94.8 \pm 9.1$  vs  $81.9 \pm 6.9$ ,  $P = 0.34$ ) or if post-dilatation was required ( $86.9 \pm 6.3$  vs  $96.6 \pm 5.3$ ,  $P = 0.42$ ), however, when pre-TAVI balloon aortic valvuloplasty was performed this resulted in a significant increase in the peak CRP ( $110.1 \pm 8.9$  vs  $51.6 \pm 3.7$ ,  $P < 0.001$ ). The development of a major vascular complication did result in a significantly increased maximal CRP release ( $153.7 \pm 11.9$  vs  $83.3 \pm 7.4$ ,  $P = 0.02$ ) and there was a trend toward a higher peak CRP following major/life-threatening bleeding ( $113.2 \pm 9.3$  vs  $82.7 \pm 7.5$ ,  $P = 0.12$ ) although this did not reach statistical significance. CRP was not found to be a predictor of 30-d mortality on univariate analysis.

**CONCLUSION:** Careful attention should be paid to baseline clinical characteristics and procedural factors when interpreting CRP following TAVI to determine their future management.

**Key words:** Aortic stenosis; Transcatheter aortic valve implantation; C reactive protein; Inflammation

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**Core tip:** Transcatheter aortic valve implantation (TAVI) results in increases in serum C reactive protein (CRP) levels reaching a peak at day 3 in all patients. CRP increase is further increased in patients with diabetes mellitus, those that underwent pre-TAVI balloon aortic valvuloplasty and patients that suffered major vascular complications. In addition to the bedside evaluation of patients, careful attention should be paid to baseline clinical characteristics and procedural factors when interpreting CRP to aid in the management and risk assessment of patients following TAVI.

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## INTRODUCTION

Aortic stenosis (AS) is the most common valvular pathology in the elderly population with a prevalence of approximately 4.6% in patients greater than 75 years of age<sup>[1]</sup>. Whilst asymptomatic AS is associated with a low mortality<sup>[2]</sup>, in those who develop symptoms, prognosis is very poor with a mortality of 50% within 2 years without treatment<sup>[3]</sup>. Whilst surgical aortic valve replacement (SAVR) remains the "gold standard" treatment, many of these elderly patients present with many co-existent comorbidities that render them inoperable or high-risk for SAVR. The emergence of transcatheter aortic valve implantation (TAVI) has revolutionised the treatment of these patients<sup>[4-8]</sup>. The transfemoral (TF) route is now the preferable TAVI vascular route due to shorter procedure and recovery times, and better clinical outcomes<sup>[9]</sup>.

In spite of TAVI being less invasive, these frail, elderly patients are at increased risk of developing complications resulting in adverse outcomes. Post-procedural infection is a potentially life-threatening complication and has been reported to occur in approximately 20% of all patients<sup>[10,11]</sup>. In combination with the clinical evaluation of patients, the C reactive protein (CRP), an acute phase protein synthesized and released by the liver is commonly measured to aid in diagnosis. However, the CRP is non-specific for infection and misinterpretation can result in misdiagnosis, inappropriate antibiotic therapy (and associated adverse effects) and prolonged in-hospital stay.

CRP is also a measure of inflammation that is thought to play a critical role in both the underlying pathogenesis of AS<sup>[12,13]</sup> with persistently high levels of circulating plasma inflammatory proteins following aortic valve intervention associated with increased cardiovascular and all-cause mortality<sup>[14,15]</sup>. SAVR results in greater activation of inflammatory pathways in comparison to TAVI with the TF access route being associated with the most attenuated inflammatory response<sup>[16]</sup>. Understanding CRP dynamics following TF TAVI is therefore critical in both the post-procedural management of these patients and predicting outcome.

The aim of this study was therefore to characterise CRP dynamics following TF TAVI and to identify clinical or procedural factors that may impact upon them.

## MATERIALS AND METHODS

### Study population

Consecutive patients that underwent TF TAVI at two hospitals (Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom and San Raffaele Scientific Institute, Milan, Italy) were included. All patients were treated for native severe AS with patients treated with TAVI devices for aortic regurgitation and for bioprosthesis degeneration excluded. A dedicated multidisciplinary "Heart Team" consisting of interven-

**Table 1 Baseline patient characteristics**

Variable	All patients (n = 208)
Age (yr)	81.4 ± 0.9
Female (%)	57 (27.4)
Diabetes mellitus (%)	34 (16.3)
Hypertension (%)	122 (58.7)
Dyslipidemia (%)	65 (31.3)
History of smoking (%)	34 (16.3)
NYHA III or IV (%)	94 (45.2)
Previous MI (%)	24 (11.5)
Previous CABG (%)	37 (17.8)
Previous PCI (%)	40 (19.2)
Cerebrovascular disease (%)	19 (9.1)
eGFR < 60 mL/min per 1.73 m <sup>2</sup> (%)	42 (20.2)
Logistic EuroScore (%)	14.8 ± 1.4

NYHA: New York Heart Association; MI: myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; eGFR: Estimated glomerular filtration rate.

tional cardiologist, cardiac surgeons, imaging specialists, general physicians and cardiac anaesthetists, discussed the management of all patients. All patients included in the study were of high surgical risk or inoperable on the basis of surgical risk scores (e.g., Euroscore) and clinical judgement to allow for other patient factors including frailty.

Daily venous plasma CRP levels were measured for up to 7 d following the procedure (or up to discharge) using.

Informed consent was provided by all patients for the procedure, subsequent clinical follow-up and analysis of data collected.

### TAVI procedure

Pre-operatively, all patients were evaluated with multi-slice computed tomography or invasive angiography to determine the presence or absence of coronary artery disease and for the characterisation of the peripheral vasculature. The choice of prosthesis (balloon expandable Edwards Sapien XT or Sapien 3 (Edwards LifeSciences, Irvine, CA, United States) or self-expandable Medtronic CoreValve or Evolut R (Medtronic, Minnesota, MN, United States) and size was at the operator's discretion. Patients treated with other devices were excluded due to their unavailability at both sites. At the time of TAVI, no patients had any clinical signs, symptoms of biochemical evidence of infection. All procedures were carried out under general anaesthesia or conscious sedation provided by a cardiac anaesthetist and were performed when possible by a fully percutaneous approach utilizing the cross-over technique and suture-mediated closure devices (Proglide and Prostar, Abbott Laboratories, IL, United States). Antibiotics were not administered to any patient routinely during the peri-operative period.

### Patient follow-up

Procedural outcomes in-hospital clinical outcomes were prospectively collected in a dedicated TAVI database. Longer-term follow-up was conducted by clinic visits.

All definition of the clinical endpoints used were in concordance with the Valve Academic Research Consortium 2 (VARC-2) definitions<sup>[17]</sup>. Patients were deemed to have infection on the basis of clinical symptoms (e.g., dysuria), signs of infection (e.g., fever) and objective evidence (e.g., elevated white cell count, positive blood culture). The administration and choice of antibiotics was at the discretion of the treating physician.

### Statistical analysis

Continuous variables are presented as the mean ± standard error of the mean. Normality of each continuous variable was tested with the Kolmogorov-Smirnov test and differences were compared using the paired *t*-test. Categorical variables are presented as numerical values and percentages and were compared using the Fisher's exact test. Cox proportional hazards regression analysis was performed to determine predictors of mortality. Receiver-operator characteristic (ROC) analysis was performed to identify the threshold for CRP as a binary classifier. All reported *P*-values were 2-sided, and values of *P* < 0.05 were regarded as statistically significant. Analyses were performed with SPSS version 21.0 (SPSS Inc., Chicago IL, United States) and GraphPad Prism version 5.0 (GraphPad, San Diego, CA, United States).

## RESULTS

### Patient population

Two hundred and eight patients underwent TF TAVI at both institutions during the study period and were included in the final analysis. The baseline characteristics of all patients are summarised in Table 1. As expected, the patient group were elderly (age: 81.4 ± 8.5 years) and of high surgical risk standard Euroscore 14.8% ± 10.4%.

### Procedural characteristics and outcomes

All patients underwent TF TAVI with an overall procedural success rate of 98.1%. Procedural characteristics are summarised: Forty-nine percent of patients received a balloon expandable device [Edwards Sapien XT (27.4%) and Edwards Sapien 3 (21.6%)] and 51% of patient received a self-expandable prosthesis [Medtronic Corevalve (37.5%) and Medtronic Evolut R (13.9%)]. Seventy-three (35.1%) patients underwent pre-TAVI balloon aortic valvuloplasty (BAV). Thirty-seven patients (17.8%) required post-dilatation following TAVI for AR with 27 patients (13%) with residual grade ≥ 2 AR at the end of the procedure. Four patients (1.9%) required emergency cardiac surgery, one patient for coronary artery obstruction, two patients for left ventricular perforation and one patient for right ventricular perforation following temporary wire placement. There were 10 (4.8%) peri-procedural deaths. Thirty-day outcomes according to the VARC-2 criteria are summarised in Table 2.

### CRP dynamics

The baseline CRP (measured in 87.7% of patients) was



**Table 2** Thirty-day outcomes

	All patients ( <i>n</i> = 208)
All-cause death	12 (5.8)
Coronary obstruction (%)	1 (0.05)
Stroke	9 (4.3)
PPM implantation	38 (18.3)
Minor vascular complication	8 (3.8)
Major vascular complication	8 (3.8)
Minor bleed	34 (16.3)
Major bleed	23 (11.1)
Life-threatening bleeding	8 (3.8)
Valve related dysfunction	0 (0)

PPM: Permanent pacemaker implantation.

8.9 ± 2.5 mg/dL for total study population. Following TAVI this significantly increased reaching a peak on day 3 of 87.6 ± 5.5 mg/dL (measured in 77.6% of patients),  $P < 0.001$  (Figure 1A). As would be expected, patients who developed clinical signs and symptoms of sepsis had significantly increased levels of CRP ( $n = 8$ ) when compared to all patients which at day 3 was 187.7 ± 6.1 representing a 21-fold increase when compared to baseline levels ( $P < 0.001$ , Figure 1B).

### Clinical impact upon CRP dynamics

Following exclusion of patients with clinical evidence of infection, peak (day 3) CRP levels were compared to determine the impact of baseline clinical factors upon maximal CRP release following TAVI. The presence of diabetes mellitus was associated with a significantly higher peak CRP level at day 3 (78.4 ± 3.2 vs 92.2 ± 4.4,  $P < 0.001$ ). The presence of hypertension (75.2 ± 4.1 vs 93.1 ± 3.2,  $P = 0.22$ ), previous PCI (70.6 ± 3.9 vs 82.2 ± 5.2,  $P = 0.39$ ), previous cardiac surgery (87.4 ± 3.1 vs 93.9 ± 3.4,  $P = 0.65$ ) or smoking (99.6 ± 3.7 vs 78.1 ± 3.3,  $P = 0.31$ ) did not impact upon the peak CRP following TAVI.

### Procedural impact upon CRP dynamics

There was no difference in peak CRP release following balloon-expandable or self-expandable TAVI implantation (94.8 ± 9.1 vs 81.9 ± 6.9,  $P = 0.34$ ) or if post-dilatation was required (86.9 ± 6.3 vs 96.6 ± 5.3,  $P = 0.42$ ). There was a difference in maximal CRP release when pre-TAVI balloon aortic valvuloplasty was performed (110.1 ± 8.9 vs 51.6 ± 3.7,  $P < 0.001$ ). Peak CRP was not found to be different between patients with residual ≥ 2 AR and those that had residual < 2 AR (71.9 ± 7.4 vs 88.9 ± 7.9,  $P = 0.28$ ). The development of a major vascular complication did result in a significantly increased maximal CRP release (153.7 ± 11.9 vs 83.3 ± 7.4,  $P = 0.02$ ) and there was a trend toward a higher peak CRP following major/life-threatening bleeding (113.2 ± 9.3 vs 82.7 ± 7.5,  $P = 0.12$ ) although this did not reach statistical significance.

### CRP as a predictive tool

Both CRP levels at baseline [hazard ratio (HR) per unit increase 0.98, 0.94-1.03,  $P = 0.42$ ] and peak levels at day 3 (HR per unit increase: 1.01, 0.98-1.02,  $P = 0.18$ ) were not found to be predictors of 30-d mortality on univariate analysis. We also did not find the magnitude of change in CRP (the difference between peak and baseline levels) to be a predictor of 30-d mortality (HR per unit increase: 0.92, 0.83-1.14,  $P = 0.33$ ). ROC analysis further confirmed that both baseline [area under the curve (AUC): 0.42] and peak levels (AUC: 0.48) of CRP was a poor predictive tool for 30-d mortality in this study population.

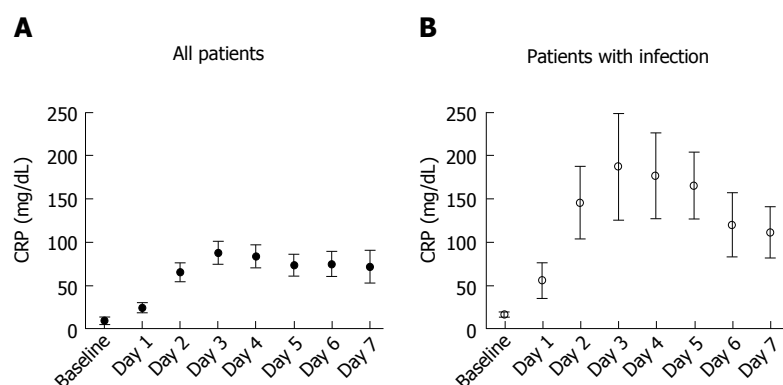
## DISCUSSION

The principal findings are: (1) CRP universally increases following TAVI reaching a peak at day 3; (2) the presence of diabetes mellitus was associated with a significant increase in the peak CRP following TAVI; (3) procedurally, the use of balloon aortic valvuloplasty during the procedure and the development of a major vascular complication resulted in a significant increase in the peak CRP; and (4) the peak CRP did not predict 30-d adverse outcomes.

Inflammation plays a central role in the pathogenesis and progression of AS<sup>[13,18,19]</sup>. The treatment of AS also results in activation of inflammatory pathways with more invasive treatment options (*e.g.*, SAVR) associated with more inflammation in comparison to less invasive treatment options (*e.g.*, TF TAVI)<sup>[16]</sup>. In addition to the magnitude of inflammation, persistently elevated markers of inflammation have been shown to be negatively associated with outcomes including mortality<sup>[14,20,21]</sup>. In agreement with previous reports, we found that CRP increased in all patients following TF TAVI reaching a peak level at day 3<sup>[16,22]</sup>.

CRP in diabetes mellitus has been shown to be a predictor of cardiovascular events and outcomes<sup>[23,24]</sup>. After excluding patients with clinical signs and symptoms of infection we found that the presence of diabetes mellitus resulted in a significantly increased peak release in CRP following TAVI. This may explain worse outcomes in this patient sub-group<sup>[25]</sup> and should be considered when interpreting CRP results following TAVI and also when counselling patients with regards to risk pre-procedurally. We did not find any other baseline clinical characteristic (*e.g.*, smoking, hypertension) to have an impact upon CRP dynamics following TAVI.

The impact of specific procedural factors upon CRP dynamics is poorly characterised in patients undergoing TF TAVI. We did not find a difference in the peak CRP between patients that were treated with a BE or SE valve possibly suggesting that they are both equally traumatic. Interestingly, the use of pre-implantation BAV was associated with a significant increase in the peak CRP at



**Figure 1** C reactive protein dynamics following transcatheter aortic valve implantation. C reactive protein (CRP) dynamics of total patient study population (A) and between patients who had clinical signs and symptoms of infections and those that did not (B).

day 3, whilst the requirement for post-dilatation or the extent of residual AR did not impact upon maximal CRP release. This finding may represent the increased trauma to the native valvular apparatus and systemic debris shower resulting in greater release of CRP, although this may also reflect disease severity of the native valve that required a BAV rather than direct valvular implantation. Nonetheless, it is important for physicians managing patients following TAVI to be aware of the procedural specifics when interpreting CRP results in the post-operative period.

Unsurprisingly, the development of a major vascular complication resulted in a greater release of CRP, likely reflecting further trauma associated with peripheral vessel intervention and also longer procedural times. The requirement for a blood transfusion, in our study population, did not impact upon CRP dynamics in the post-procedural period.

CRP has been shown to be a useful prognostic tool<sup>[22]</sup> following TAVI, however in our study population, this was not found to be the case, possibly due to the relative small numbers of patients and short follow-up.

### Study limitations

This study has some limitations. This was a retrospective study with treatment strategy (*e.g.*, prosthesis selection, use of BAV) at the operator's discretion and so the effect of selection bias cannot be excluded. Patient numbers were relatively small with limited follow-up and so the study may be underpowered to detect the predictive value of CRP upon outcomes. Finally, we did not measure the role of other markers of inflammation that in combination with CRP may have augmented its usefulness, although this study reflects routine clinical practice and makes the results directly applicable to a contemporary TAVI service.

In conclusion, TAVI results in increases in serum CRP levels reaching a peak at day 3 in all patients. CRP increase is further increased in patients with diabetes mellitus, those that underwent pre-TAVI BAV and patients that suffered major vascular complications. In addition to the bedside evaluation of patients, careful attention should be paid to baseline clinical characteristics and

procedural factors when interpreting CRP to aid in the management and risk assessment of patients following TAVI.

## COMMENTS

### Background

Transcatheter aortic valve implantation (TAVI) is now the established treatment of choice for the management of patients presenting with severe symptomatic aortic stenosis (AS) who are deemed inoperable or of high surgical risk. The post-procedural management of these patients is complex due to their concomitant comorbidities. In combination with the clinical evaluation of patients, the C reactive protein (CRP), is commonly measured to aid in diagnosis. However, the CRP is non-specific for infection and misinterpretation can result in misdiagnosis, inappropriate antibiotic therapy (and associated adverse effects) and prolonged in-hospital stay. Understanding CRP dynamics following TAVI is therefore critical in the post-procedural management of these patients.

### Research frontiers

The role of inflammation in both the pathogenesis of AS and its roles in repair, recovery and predicting outcomes following TAVI are currently important areas of investigation in this area.

### Innovations and breakthroughs

This study demonstrates that CRP levels increase in all patients following TAVI but we here identify both specific patient and procedural factors that may result in a greater magnitude of change in CRP, that should be considered in the management of these complex patients in the post-operative period.

### Applications

The findings of this study highlight the importance of taking into consideration not only the clinical condition of the patient but also baseline patient characteristics and procedural factors when interpreting CRP levels following TAVI. Into the future, research will focus on interventions to reduce inflammation peri- and post-procedurally to investigate if this will have an effect on outcomes.

### Terminology

TAVI is a technique by which a bioprosthetic aortic valve can be implanted in a minimally invasive fashion by delivering a catheter-mounted valve to the aortic annulus. The CRP is an acute phase protein synthesized and released by the liver.

### Peer-review

The study was nicely executed and the text is well written.

## REFERENCES

- 1 Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-

- based study. *Lancet* 2006; **368**: 1005-1011 [PMID: 16980116 DOI: 10.1016/S0140-6736(06)69208-8]
- 2 **Pellikka PA**, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005; **111**: 3290-3295 [PMID: 15956131 DOI: 10.1161/CIRCULATIONAHA.104.495903]
- 3 **Ross J**, Braunwald E. Aortic stenosis. *Circulation* 1968; **38**: 61-67 [PMID: 4894151 DOI: 10.1161/01.cir.38.1s5.v-61]
- 4 **Leon MB**, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; **363**: 1597-1607 [PMID: 20961243 DOI: 10.1056/NEJMoa1008232]
- 5 **Kapadia SR**, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, Webb JG, Mack MJ, Douglas PS, Thourani VH, Babaliaros VC, Herrmann HC, Szeto WY, Pichard AD, Williams MR, Fontana GP, Miller DC, Anderson WN, Akin JJ, Davidson MJ, Smith CR. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015; **385**: 2485-2491 [PMID: 25788231 DOI: 10.1016/S0140-6736(15)60290-2]
- 6 **Mack MJ**, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015; **385**: 2477-2484 [PMID: 25788234 DOI: 10.1016/S0140-6736(15)60308-7]
- 7 **Smith CR**, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; **364**: 2187-2198 [PMID: 21639811 DOI: 10.1056/NEJMoa1103510]
- 8 **Adams DH**, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014; **370**: 1790-1798 [PMID: 24678937 DOI: 10.1056/NEJMoa1400590]
- 9 **Conrotto F**, D'Ascenzo F, Francesca G, Colaci C, Sacciatella P, Biondi-Zoccai G, Moretti C, D'Amico M, Gaita F, Marra S. Impact of access on TAVI procedural and midterm follow-up: a meta-analysis of 13 studies and 10,468 patients. *J Interv Cardiol* 2014; **27**: 500-508 [PMID: 25196312 DOI: 10.1111/joic.12141]
- 10 **van der Boon RM**, Nuis RJ, Benitez LM, Van Mieghem NM, Perez S, Cruz L, van Geuns RJ, Serruys PW, van Domburg RT, Dager AE, de Jaegere PP. Frequency, determinants and prognostic implications of infectious complications after transcatheter aortic valve implantation. *Am J Cardiol* 2013; **112**: 104-110 [PMID: 23566540 DOI: 10.1016/j.amjcard.2013.02.061]
- 11 **Falcone M**, Russo A, Mancone M, Carrierio G, Mazzesi G, Miraldi F, Pennacchi M, Pugliese F, Tritapepe L, Vullo V, Fedele F, Sardella G, Venditti M. Early, intermediate and late infectious complications after transcatheter or surgical aortic-valve replacement: a prospective cohort study. *Clin Microbiol Infect* 2014; **20**: 758-763 [PMID: 24267878]
- 12 **Mohler ER**, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. *Circulation* 2001; **103**: 1522-1528 [PMID: 11257079 DOI: 10.1161/01.CIR.103.11.1522]
- 13 **Kaden JJ**, Dempfle CE, Grobholz R, Fischer CS, Vocke DC, Kiliç R, Sarikoç A, Piñol R, Hagl S, Lang S, Brueckmann M, Borggrefe M. Inflammatory regulation of extracellular matrix remodeling in calcific aortic valve stenosis. *Cardiovasc Pathol* 2005; **14**: 80-87 [PMID: 15780799]
- 14 **Schewel D**, Frerker C, Schewel J, Wohlmuth P, Meincke F, Thielsen T, Kreidel F, Kuck KH, Schäfer U. Clinical impact of paravalvular leaks on biomarkers and survival after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2015; **85**: 502-514 [PMID: 24259366]
- 15 **Husser O**, Núñez J, Núñez E, Holzamer A, Camboni D, Luchner A, Sanchis J, Bodi V, Riegger GA, Schmid C, Hilker M, Hengstenberg C. Tumor marker carbohydrate antigen 125 predicts adverse outcome after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2013; **6**: 487-496 [PMID: 23702013 DOI: 10.1016/j.jcin.2013.02.006]
- 16 **Erdos G**, Lippuner C, Kocsis I, Schiff M, Stucki M, Carrel T, Windecker S, Eberle B, Stueber F, Book M. Technical Approach Determines Inflammatory Response after Surgical and Transcatheter Aortic Valve Replacement. *PLoS One* 2015; **10**: e0143089 [PMID: 26599610 DOI: 10.1371/journal.pone.0143089]
- 17 **Kappetein AP**, Head SJ, Gènéreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012; **60**: 1438-1454 [PMID: 23036636 DOI: 10.1016/j.jacc.2012.09.001]
- 18 **Imai K**, Okura H, Kume T, Yamada R, Miyamoto Y, Kawamoto T, Watanabe N, Neishi Y, Toyota E, Yoshida K. C-Reactive protein predicts severity, progression, and prognosis of asymptomatic aortic valve stenosis. *Am Heart J* 2008; **156**: 713-718 [PMID: 18926152 DOI: 10.1016/j.ahj.2008.04.011]
- 19 **Galante A**, Pietroiusti A, Vellini M, Piccolo P, Possati G, De Bonis M, Grillo RL, Fontana C, Favalli C. C-reactive protein is increased in patients with degenerative aortic valvular stenosis. *J Am Coll Cardiol* 2001; **38**: 1078-1082 [PMID: 11583885 DOI: 10.1016/S0735-1097(01)01484-X]
- 20 **Dahl JS**, Videbæk L, Poulsen MK, Rudbæk TR, Christensen NL, Pellikka PA, Rasmussen LM, Møller JE. Relation of osteoprotegerin in severe aortic valve stenosis to postoperative outcome and left ventricular function. *Am J Cardiol* 2013; **112**: 1433-1438 [PMID: 23871267 DOI: 10.1016/j.amjcard.2013.06.015]
- 21 **Sinning JM**, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Müller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. *Eur Heart J* 2012; **33**: 1459-1468 [PMID: 22285582 DOI: 10.1093/eurheartj/ehs002]
- 22 **Krumsdorf U**, Chorianopoulos E, Plegier ST, Kallenbach K, Karck M, Katus HA, Bekerredjian R. C-reactive protein kinetics and its prognostic value after transfemoral aortic valve implantation. *J Invasive Cardiol* 2012; **24**: 282-286 [PMID: 22684383]
- 23 **Pfützner A**, Forst T. High-sensitivity C-reactive protein as cardiovascular risk marker in patients with diabetes mellitus. *Diabetes Technol Ther* 2006; **8**: 28-36 [PMID: 16472048 DOI: 10.1089/dia.2006.8.28]
- 24 **Tabák AG**, Kivimäki M, Brunner EJ, Lowe GD, Jokela M, Akbaraly TN, Singh-Manoux A, Ferrie JE, Witte DR. Changes in C-reactive protein levels before type 2 diabetes and cardiovascular death: the Whitehall II study. *Eur J Endocrinol* 2010; **163**: 89-95 [PMID: 20573938]
- 25 **Conrotto F**, D'Ascenzo F, Giordana F, Salizzoni S, Tamburino C, Tarantini G, Presbitero P, Barbanti M, Gasparetto V, Mennuni

M, Napodano M, Rossi ML, La Torre M, Ferraro G, Omedè P, Scacciatella P, Marra WG, Colaci C, Biondi-Zoccai G, Moretti C, D'Amico M, Rinaldi M, Gaita F, Marra S. Impact of diabetes mellitus

on early and midterm outcomes after transcatheter aortic valve implantation (from a multicenter registry). *Am J Cardiol* 2014; **113**: 529-534 [PMID: 24315111 DOI: 10.1016/j.amjcard.2013.10.025]

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## Rare presentation of intralobar pulmonary sequestration associated with repeated episodes of ventricular tachycardia

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**Author contributions:** Rao DS had suggested the line of management; Barik R had done the procedure and written the manuscript.

**Institutional review board statement:** This case report was won the approval of the institutional ethical committee and the Review Board standards at Nizam's Institute of Medical Sciences, Hyderabad, India.

**Informed consent statement:** The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

**Conflict-of-interest statement:** None.

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### Abstract

Arterial supply of an intralobar pulmonary sequestration (IPS) from the coronary circulation is extremely rare. A significant coronary steal does not occur because of dual or triple sources of blood supply to sequestered lung tissue. We present a 60-year-old woman who presented to us with repeated episodes of monomorphic ventricular tachycardia (VT) in last 3 mo. Radio frequency ablation was ineffective. On evaluation, she had right lower lobe IPS with dual arterial blood supply, *i.e.*, right pulmonary artery and the systemic arterial supply from the right coronary artery (RCA). Stress myocardial perfusion scan revealed significant inducible ischemia in the RCA territory. Coronary angiogram revealed critical stenosis of proximal RCA just after the origin of the systemic artery supplying IPS. The critical stenosis in the RCA was stented. At 12 mo follow-up, she had no further episodes of VT or angina.

**Key words:** Coronary steal; Coronary artery disease; Ventricular tachycardia; Angioplasty; Intralobar pulmonary sequestration

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**Core tip:** The intralobar pulmonary sequestration (IPS) of right lower lobe of the lung (RLL) is less than 10% of all the pulmonary sequestration. It is rare to encounter that right coronary artery is being the source of systemic arterial supply to IPS of RLL. This anomalous artery was the reason for ischemia in the area subtended by right

coronary artery (RCA) by coronary steal phenomenon. A significant stenosis of RCA just distal to origin of the anomalous artery supplying the IPS is extremely rare which was further worsening ischemia by incremental steal. We felt excessive stealing from RCA was the reason for ischemic ventricular tachycardia in this patient. Angioplasty of right coronary stenosis relieved ischemia in the area subtended by RCA by removing obstruction and reducing coronary steal.

Rao DS, Barik R. Rare presentation of intralobar pulmonary sequestration associated with repeated episodes of ventricular tachycardia. *World J Cardiol* 2016; 8(7): 432-435 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v8/i7/432.htm> DOI: <http://dx.doi.org/10.4330/wjc.v8.i7.432>

## INTRODUCTION

Pulmonary sequestration consists 0.5%-6.4% of all congenital malformation of lung<sup>[1]</sup>. Intralobar pulmonary sequestration (IPS) accounts for 75%-90% of the total pulmonary sequestration<sup>[1,2]</sup>. Right lower lobe is involved in 20% of cases of IPS<sup>[3]</sup>. The non-functioning mass of lung tissue that lacks normal communication with the tracheobronchial tree is supplied by systemic circulation (nutritional branches from abdominal or thoracic aorta) or dual arterial supply (systemic artery and pulmonary artery)<sup>[4]</sup> or triple arterial supply (systemic, pulmonary and bronchial artery)<sup>[5]</sup>. Pulmonary sequestration supplied by a normal coronary artery is extremely rare with significant coronary steal<sup>[6]</sup> or coronary artery disease<sup>[7]</sup>. Right coronary artery (RCA) is very rarely being the source of blood supply when compared to the left circumflex coronary artery.

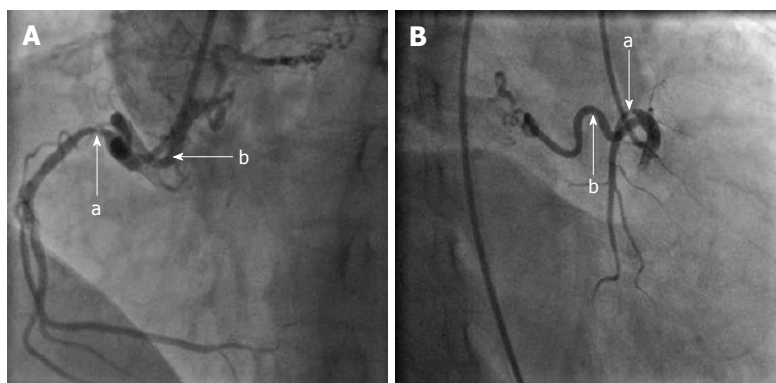
## CASE REPORT

A 60-year-old female was referred to us for repeated episodes of monomorphic ventricular tachycardia (VT) in the last 12 mo. She had undergone recently radio-frequency ablation (RFA) for VT. Coronary angiogram prior to RFA was reported to have mild RCA disease as was mentioned in referral slip. Her past history reveals she was a known case of right lower lobe IPS accidentally detected in contrast enhanced computed tomography (CECT) of chest when she was under evaluation for right lower lobe pneumonia. The detail of arterial supply to sequestration was evident from the report of past CECT chest. At admission, 12 leads electrocardiography and echocardiogram were normal. A chest X-ray revealed nonhomogenous opacity of right lower lobe. Myocardial stress perfusion scan was positive for inducible ischemia in the RCA territory. Her coronary angiogram showed critical stenosis of proximal dominant RCA (Figure 1A). The anomalous artery to the right sided IPS was just before the critical RCA stenosis (Figure 1B). The follow-

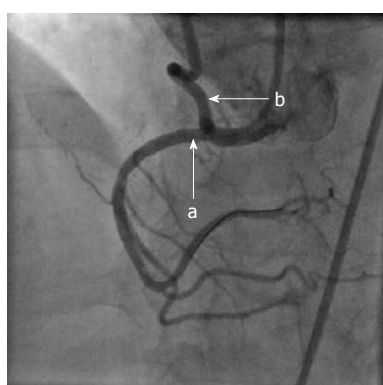
up in levophase confirmed normal pulmonary venous drainage [Video core tip: Selective RCA angiogram in left anterior oblique 48 degrees (LAO 48°) showed the normal venous drainage from IPS to right lower pulmonary vein]. The lesion in RCA was stented using a drug eluting stent, 3 mm × 12 mm, Xience V (Abbott's Vascular) with predilatation with a noncompliant coronary balloon (Figure 2). Angioplasty of right coronary stenosis relieved ischemia in the area subtended by RCA by removing obstruction to forward flow and coronary steal. At 12 mo follow-up, she had no further episodes of VT and angina. The elective resection of IPS was planned in future as the patient was not willing to undergo surgery at present.

## DISCUSSION

In most cases, IPS has a single feeding artery. Sometimes, there are multiple systemic arteries supply to IPS. Arterial supply of pulmonary sequestration mainly originates from thoracic aorta (46.1%-86.1%) and abdominal aorta (6.9%-31.6%)<sup>[8-10]</sup>. The other feeders are intercostal artery, phrenic artery, branches from aortic arch, subclavian artery, pulmonary artery, left gastric artery, coronary artery, celiac trunk and renal artery<sup>[8-10]</sup>. Several complications related to IPS include recurrent pulmonary infections, haemoptysis and heart failure from persistent left-to-right shunt. The natural history of sequestration supplied by a coronary artery remains unknown because of rare incidence. In absence of complications, surgical resection is controversial<sup>[11]</sup> and the exact timing of such surgery is not known<sup>[12]</sup>. A recent series suggest surgical resection is safe in such cases because of very lower complication rate<sup>[13]</sup>. Recently, some researchers suggest to resect the sequestration to avoid unpredictable fatal haemoptysis<sup>[14]</sup>. Surgical resection is recommended for recurrent pulmonary infections or coronary steal. In our case, the detection of IPS was incidental, *i.e.*, detection during evaluation for pneumonia. Significant coronary artery disease of the of the feeder that nourishes IPS is extremely rare<sup>[15]</sup>. The unique finding in our case was significant coronary steal due to critical stenosis of RCA just distal to the origin of artery which was feeding IPS contributing to significant ischemia in the area subtended by RCA which is the very reason for ischemic VT in our case. The various management approaches in a case are option 1: Surgical resection of IPS, ligation of abnormal feeder and distal RCA graft; option 2: Angioplasty of RCA and elective resection of IPS with ligation of feeder; or option 3: Coil embolization of feeder artery during angioplasty of RCA and elective resection of sequestration. The patient was not willing for lung surgery during current admission, therefore, the best option was coiling of feeder to IPS during angioplasty of RCA. As there was one episode of pneumonia in our patient, we proceeded with the angioplasty of RCA which was the needed most at the time presentation. Therefore, our future plan for our patient is ligation of the



**Figure 1** Selective right coronary angiogram from right femoral approach in left anterior oblique 48 degrees and right posterior caudal view showed tight right coronary artery (A) and aberrant blood supply to right lower lobe intralobar sequestration which the branch of right coronary artery (B).



**Figure 2** Selective right coronary angiogram after stenting the proximal lesion left anterior oblique 48 degrees (a) which resulted in significant reduction of flow in aberrant blood supply to right lower lobe intralobar sequestration (b).

feeder artery during the resection of IPS.

## COMMENTS

### Case characteristics

This is 62-year-old female with previous diagnosis of intralobar sequestration of right lower lobe presented with repeated episodes of ventricular tachycardia (VT) without any response to radiofrequency ablation therapy.

### Clinical diagnosis

Repeated episodes of VT.

### Differential diagnosis

Coronary artery disease, ischemic VT, idiopathic VT and cardiomyopathy.

### Laboratory diagnosis

Right lower lobe intrapulmonary sequestration associated with critical stenosis of right coronary artery (RCA).

### Imaging diagnosis

Selective coronary angiogram confirms the diagnosis of critical RCA stenosis associated a branch of right coronary supplying right intralobar pulmonary sequestration (IPS).

### Pathological diagnosis

Contrast enhanced computed tomography is suggestive of right lower lobe

intrapulmonary sequestration.

### Treatment

RCA angioplasty with future plan of resection of intrapulmonary sequestration.

### Related reports

Symptomatic IPS should undergo elective surgical resection with ligation of systemic arterial supply to the sequestered lung.

### Term explanation

Pulmonary sequestration is a rare congenital malformation of the lower respiratory tract. It consists of a nonfunctioning mass of normal lung tissue that lacks normal communication with the tracheobronchial tree, and that receives its arterial blood supply from the systemic circulation. It is of three types: IPS, extralobar pulmonary sequestration and bronchopulmonary-foregut malformation.

### Experiences and lessons

RCA as source of systemic blood supply to the right IPS is rare. If the same coronary artery acquires coronary artery stenosis distal to the systemic feeder artery to sequestration, it further worsens the ischemia in the RCA territory. The resection of sequestered lung, ligation of systemic artery to sequestration and coronary artery bypass graft is the ideal treatment in such situation.

### Peer-review

This is an interesting and very unusual case.

## REFERENCES

- 1 **Gompelmann D**, Eberhardt R, Heussel CP, Hoffmann H, Diemann H, Schuhmann M, Böckler D, Schnabel PA, Warth A, Lopez-Benitez R, Herth FJ. Lung sequestration: a rare cause for pulmonary symptoms in adulthood. *Respiration* 2011; **82**: 445-450 [PMID: 21311173 DOI: 10.1159/000323562]
- 2 **Conran RM**, Stocker JT. Extralobar sequestration with frequently associated congenital cystic adenomatoid malformation, type 2: report of 50 cases. *Pediatr Dev Pathol* 1999; **2**: 454-463 [PMID: 10441623 DOI: 10.1007/s100249900149]
- 3 **Wei Y**, Li F. Pulmonary sequestration: a retrospective analysis of 2625 cases in China. *Eur J Cardiothorac Surg* 2011; **40**: e39-e42 [PMID: 21459605 DOI: 10.1016/j.ejcts.2011.01.080]
- 4 **Barik R**, Patnaik AN, Malempati AR, Nemani L. Pryce type I sequestration: no mosquito shooting. *Asian Cardiovasc Thorac Ann* 2015; **23**: 567-569 [PMID: 24585298 DOI: 10.1177/0218492314522471]
- 5 **Theodoropoulos I**, Schwartz MZ. Intralobar pulmonary sequestration: an uncommon case with triple arterial supply and systemic venous drainage. *Pediatr Surg Int* 2012; **28**: 741-744 [PMID: 22441623 DOI: 10.1007/s00381-012-1000-0]

- 22526550 DOI: 10.1007/s00383-012-3088-4]
- 6 **Temes RT**, Talbot WA, Carrillo YM, Keck GM, Wernly JA. Sequestration of the lung arising from the circumflex coronary artery. *Ann Thorac Surg* 1998; **65**: 257-259 [PMID: 9456133 DOI: 10.1016/S0003-4975(97)01263-0]
- 7 **Marinos T**, Bitzikas G, Madesis A, Galanos O. Sequestered hypoplastic pulmonary lobe supplied by the circumflex coronary artery in a patient with coronary artery disease: a case report. *Heart Surg Forum* 2006; **9**: E565-E567 [PMID: 16467062 DOI: 10.1532/HSF98.20051039]
- 8 **Savic B**, Birtel FJ, Tholen W, Funke HD, Knoche R. Lung sequestration: report of seven cases and review of 540 published cases. *Thorax* 1979; **34**: 96-101 [PMID: 442005 DOI: 10.1136/thx.34.1.96]
- 9 **Sun X**, Xiao Y. Pulmonary sequestration in adult patients: a retrospective study. *Eur J Cardiothorac Surg* 2015; **48**: 279-282 [PMID: 25361546 DOI: 10.1093/ejcts/ezu397]
- 10 **Xie D**, Xie H, You X, Chen C, Jiang G. Pulmonary sequestration with aberrant arteries arising from the renal artery and the internal thoracic artery. *Ann Thorac Surg* 2013; **96**: e131 [PMID: 24182513 DOI: 10.1016/j.athoracsur.2013.08.018]
- 11 **Laberge JM**, Puligandla P, Flageole H. Asymptomatic congenital lung malformations. *Semin Pediatr Surg* 2005; **14**: 16-33 [PMID: 15770585 DOI: 10.1053/j.sempedsurg.2004.10.022]
- 12 **Gezer S**, Taştepe I, Sirmali M, Findik G, Türüt H, Kaya S, Karaoğlu N, Cetin G. Pulmonary sequestration: a single-institutional series composed of 27 cases. *J Thorac Cardiovasc Surg* 2007; **133**: 955-959 [PMID: 17382633 DOI: 10.1016/j.jtcvs.2006.11.003]
- 13 **Wang LM**, Cao JL, Hu J. Video-assisted thoracic surgery for pulmonary sequestration: a safe alternative procedure. *J Thorac Dis* 2016; **8**: 31-36 [PMID: 26904209]
- 14 **Walker CM**, Wu CC, Gilman MD, Godwin JD, Shepard JA, Abbott GF. The imaging spectrum of bronchopulmonary sequestration. *Curr Probl Diagn Radiol* 2014; **43**: 100-114 [PMID: 24791614 DOI: 10.1067/j.cpradiol.2014.01.005]
- 15 **Fernandez-Vega A**, Vilacosta I, Vedia OA, Pedraja I, Vivas D, Martinez-Vives P. A 'kidnapper' left circumflex coronary artery. *Eur Heart J* 2016; **37**: 919 [PMID: 26705384]

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