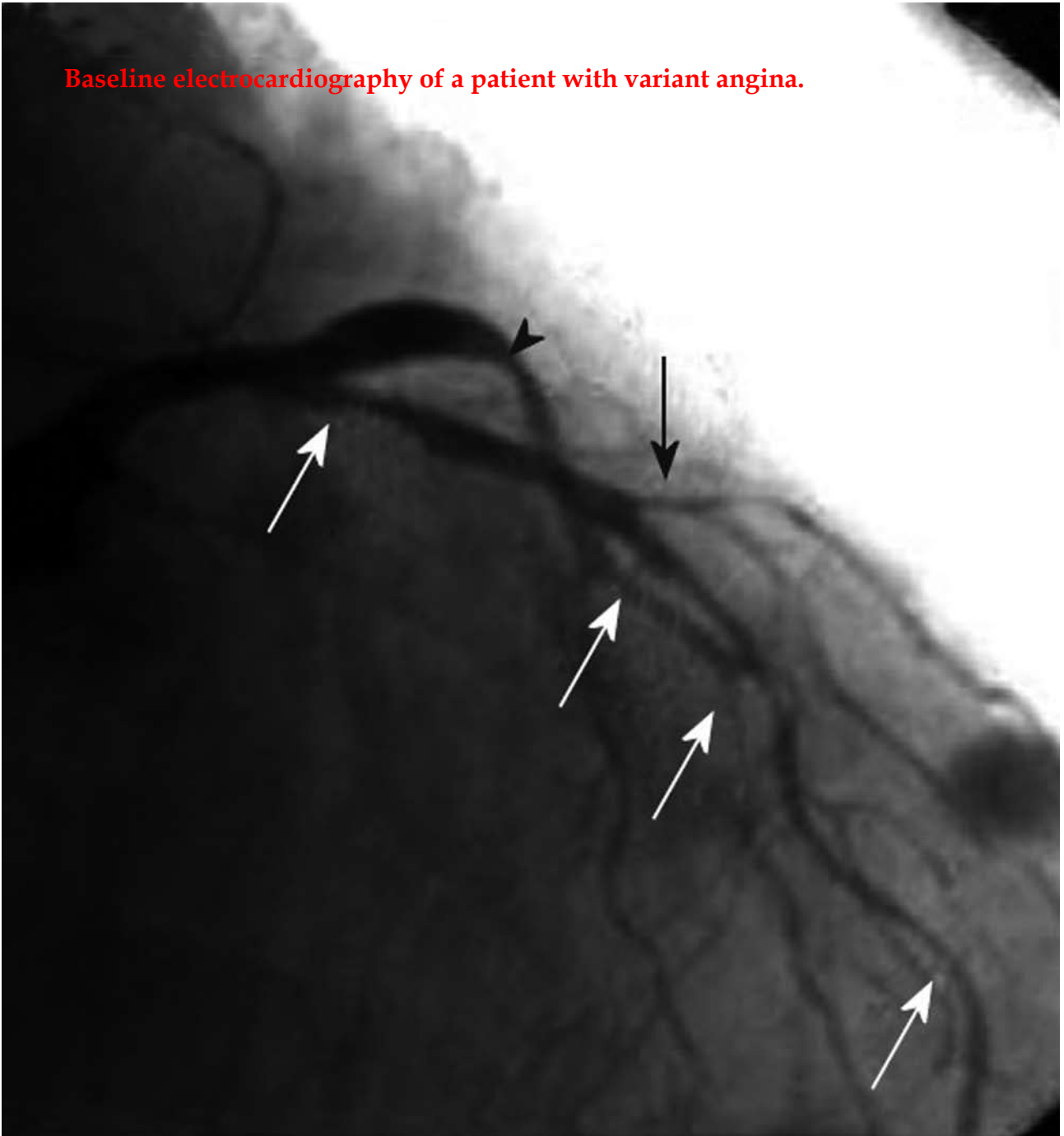


Baseline electrocardiography of a patient with variant angina.





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Use of the impedance threshold device in cardiopulmonary resuscitation

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Abstract

Although approximately one million sudden cardiac deaths occur yearly in the US and Europe, cardiac arrest (CA) remains a clinical condition still characterized by a poor prognosis. In an effort to improve the cardiopulmonary resuscitation (CPR) technique, the 2005 American Heart Association (AHA) Guidelines for CPR gave the impedance threshold device (ITD) a Class IIa recommendation. The AHA recommendation means that there is strong evidence to demonstrate that ITD enhances circulation, improves hemodynamics and increases the likelihood of resuscitation in patients in CA. During standard CPR, venous blood return to the heart relies on the natural elastic recoil of the chest which creates a transient decrease in intrathoracic pressure. The ITD further decreases intrathoracic pressure by preventing respiratory gases from entering the lungs during the decompression phase of CPR. Thus, although ITD is placed into the respiratory circuit

it works as a circulatory enhancer device that provides its therapeutic benefit with each chest decompression. The ease of use of this device, its ability to be incorporated into a mask and other airway devices, the absence of device-related adverse effects and few requirements in additional training, suggest that ITD may be a favorable new device for improving CPR efficiency. Since the literature is short of studies with clinically meaningful outcomes such as neurological outcome and long term survival, further evidence is still needed.

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Key words: Cardiopulmonary resuscitation; Coronary perfusion pressure; Impedance threshold device; Return of spontaneous circulation; Survival

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INTRODUCTION

Although the term cardiopulmonary resuscitation (CPR) was first published 50 years ago, the origins of resus-

citation extend back centuries. Various methods of resuscitation have been used throughout the ages with the oldest example from around 3000 BC, being the introduction of smoke into the rectum as depicted in hieroglyphics and cave drawings of the Mayan and Inca people of South and Central America. The first apparent attempt of resuscitation was recorded in the Bible around 800 BC and was Elijah's mouth to mouth ventilation^[1].

Very early in our history, people realized that the body became cold when lifeless, and therefore connected heat with life. In order to prevent death, the body was warmed. The use of warm ashes, burning excrement, or hot water placed directly on the body were all employed in an attempt to restore life^[2].

The first report of an experimental intubation of the trachea was probably by the great Muslim philosopher and physician Avicenna around the year 1000^[3]. "When necessary, a cannula of gold, silver or another suitable material is advanced down the throat to support inspiration." In 1543, Vesalius *et al*^[4] published "De humani corporis fabrica" which described blowing into a tube to resuscitate an animal.

During Enlightenment, starting around 1750, Goodwin and Kite hypothesized that asphyxia causes the heart to stop. Kite suggested electric shock treatment (defibrillation), but airway problems produced by the tongue were not appreciated at that time^[5]. Marshall Hall was the first to realize that leaving the victim supine allows the tongue to fall backwards blocking the airway and he supported the notion that the prone position should be employed in resuscitation^[6].

In the year 1957, Dr. Peter Safar, in a series of elegant and daring experiments on curarized volunteers, showed that tilting the head could open the airway and that the mouth-to-mouth technique of artificial ventilation was superior over all others techniques described before^[7,8]. Three years later Kouwenhoven *et al*^[9] published a paper on closed-chest cardiac "massage", after observing that chest compressions produced arterial pulses. They confirmed the usefulness of chest compressions by performing experiments with anesthesia-induced cardiac arrests.

Modern published studies report that about one million people suffer cardiac arrest (CA) each year in the United States and Europe, almost one every 30 s. Many of them will undergo CPR by bystanders and emergency medical services (EMS) in a desperate attempt to restore life. Unfortunately, according to recent literature, only 1 in 5 adults survive in-hospital CA while less than 1 in 10 adults survive out-of-hospital CA^[10-13]. These statistics are somewhat sobering, especially when compared with survival rates of the first resuscitative techniques ever developed and reported^[14].

In addition, recent statistics on neurological recovery after resuscitation are also disappointing when put into historical perspective. Stephenson *et al*^[14] reported that 56% of the 1200 CA victims were successfully resuscitated, and only 8 of these patients were rendered

decerebrate. Furthermore, the first successful human defibrillation, in 1947, involved CPR for over an hour, and yet the patient had no long-term neurological deficits^[15]. Neurological injury after resuscitation of a witnessed CA victim means that CPR efforts failed to provide sufficient cerebral blood flow. Needless to say, novel CPR techniques should achieve not only cardiopulmonary but also neurological recovery.

A number of new mechanical devices have been developed in recent years to improve the present dismal outcomes for patients in CA^[16]. The 2005 American Heart Association (AHA) guidelines gave the impedance threshold device (ITD) a Class IIa recommendation^[17]. The AHA recommendation means that there is strong evidence to demonstrate that the ITD (Figure 1) enhances circulation, improves hemodynamics and increases the likelihood of resuscitation of CA victims. It is the most highly recommended CPR adjunct and carries a higher recommendation than any medication used in adult CPR.

CORONARY PERFUSION PRESSURE AND BLOOD FLOW

Various studies have shown that coronary perfusion pressure (CPP), generated during CPR, is the only key component for successful resuscitation. CPP is the pressure gradient between the ascending aorta and the right atrium during the "diastolic" or decompression phase of CPR. Like the physiology of normal sinus rhythm, myocardial blood flow occurs only during the artificial diastole or the chest relaxation phase of CPR. An increased right atrial pressure may impede venous return of myocardial blood flow to the right atrium. This impeding pressure must be subtracted from the driving pressure (aortic diastolic pressure) to calculate the perfusion pressure gradient^[18].

CPP has been correlated with myocardial blood flow generated during CPR and both successful resuscitation and return of spontaneous circulation (ROSC)^[19-21]. Kitakaze *et al*^[22] clearly shows that successful resuscitation is correlated with both the CPP produced and the resultant left ventricular myocardial blood flow. Furthermore, CPP has been associated with longer-term outcomes including from 1 to 24-h survival and even 7-d survival^[23-25].

PHYSIOLOGY OF CPR

The objective of any CPR effort is to pump blood from the heart to the vital organs with each chest compression and to enhance the return of blood back to the heart with each chest relaxation. Two different theories attempt to explain the mechanism of blood flow during CPR^[26].

The "cardiac pump theory" is based on the concept that the heart is compressed between the spinal column and the sternum during chest compressions^[27]. This theory requires that the atrioventricular valves be closed during cardiac compression (systole).



Figure 1 The impedance threshold device.



Figure 2 The impedance threshold device attached to the endotracheal tube of an intubated manikin.

On the other hand, in the “thoracic pump theory”, external pressure on the chest causes an increase in intrathoracic pressure without direct compression of the heart with the latter acting as a passive conduit^[28]. This theory requires that the atrioventricular valves be open during cardiac compression. The increase in intrathoracic pressure is evenly distributed over all heart chambers and intrathoracic vascular structures. Therefore, a pressure gradient towards the aorta is generated, resulting in forward blood flow. In fact, during the compression phase of CPR the intrathoracic pressure rises from 5-25 mmHg. This positive pressure forces blood out of the heart to vital organs. However, the compression phase is only half of the duty cycle. During chest wall relaxation, intrathoracic pressure falls to approximately -5 mmHg^[29]. This decrease in intrathoracic pressure to sub-atmospheric levels creates a vacuum relative to the rest of the body, sufficient to propel some movement of venous blood from the periphery back into the right heart. This is a very critical phase because if the heart is not filled with blood there would not be sufficient blood circulated forward in the next chest compression. It is also during the decompression phase that the coronary arteries supply the heart muscle with blood^[30].

Furthermore, with each chest compression the respiratory gases are actively pushed out of the thorax. On the other hand, during the decompression phase the intrathoracic vacuum works like suction and draws not only blood back into the heart, but also some air back into the lungs. Unfortunately, much of the potential hemodynamic benefit of this vacuum is lost due to the influx of inspiratory gases. Moreover, each time the chest wall recoils a transient decrease in intracranial pressure occurs^[31-33].

ITD

Clinically, venous blood flow is increased by the Mueller maneuver, a technique in which inspiration is performed when the trachea is simultaneously occluded by the epiglottis^[34]. It is this principle that is further exploited by the ITD in an attempt to further decrease intrathoracic pressure and thus enhance venous return in CPR. The ITD is a small (35 mL), single use, disposable plastic valve that can be attached to a tracheal tube (Figure 2), a

face mask, a laryngeal mask or any other protective airway device and must be placed at the respiratory circuit as soon as it becomes available. It has been demonstrated that its effectiveness is the same whether it is used with a face mask or an endotracheal tube^[35]. It contains a silicon diaphragm designed to selectively impede inspiratory airflow into the patient when the intrathoracic pressure is less than 0 atm. Hence, as soon as the chest wall recoils back to its resting position the diaphragm occludes the lumen within the valve, preventing all unnecessary air from entering the chest when the patient is not being actively ventilated. This creates and maintains a vacuum within the chest that further improves venous return back into the heart. The maximum negative intrathoracic pressure generated in animal studies ranged from -4 to -8 mmHg while in an intubated patient was -13^[36-38]. Without the ITD, intrathoracic pressure was only -3 mmHg^[38]. It takes as many as 5 compression/decompression cycles to achieve the maximum negative intrathoracic pressure. Thus, despite its placement into the ventilation circuit, the ITD is a circulatory enhancer device that provides its therapeutic benefit with each chest decompression.

During active ventilation by the rescuer, the lumen within the ITD remains open and there is no resistance to ventilation. Similarly, with chest compression, there is no resistance to the movement of air out of the chest^[39]. Spontaneous inspiration through the ITD is possible but may be difficult for a recently resuscitated patient. Cracking pressure, which is the inspiratory pressure necessary to open the valve and allow for spontaneous inspiration within the device, can vary at the time of manufacture. Clinical trials to date have been performed with ITD cracking pressures between -15 cm and -24 cm H₂O^[40]. This cracking pressure could increase substantially the work of breathing in a spontaneously breathing subject and it is therefore recommended that the device be removed as soon as subjects start breathing spontaneously.

Furthermore, ResQPOD (newer model ITD) has 2 ventilation timing assist lights on its upper surface. They provide guidance on the correct ventilation rate, when a secured airway has been placed, by flashing 12 times a minute. This visual aid works to avoid hyperventilation given that increased ventilation rates during CPR affect

venous return to the heart, resulting in reduced aortic blood pressure and coronary perfusion pressure^[31,32]. Moreover, each time active positive-pressure ventilation is delivered, the decompression phase intrathoracic vacuum is destroyed and requires regeneration^[40]. Thus, the less frequent the ventilation rate, the greater the blood flow back to the heart. The ResQPOD's inspiratory impedance feature is independent of the timing lights and inspiratory impedance is provided whether the lights are ON or OFF.

ANIMAL STUDIES

The ResQPOD has been the subject of over 30 clinical trials and animal studies. The first experiments designed to test the impedance valve concept were performed in a pig model of CA.

Standard CPR combined with an ITD

In a study by Lurie *et al*^[41], 22 pigs were left untreated for 6 min after induction of ventricular fibrillation. CPR efforts were then performed with either standard CPR plus a sham valve ($n = 11$) or standard CPR plus a functional valve ($n = 11$). Use of the functional ITD during standard CPR significantly improved vital organ blood flow and total left ventricular blood flow. Moreover, CPP and cerebral blood flow were higher in the animals treated with the functional valve. An interesting protocol was one in which the ITD was added or removed in a sequential manner in the same animal during the performance of CPR^[29]. Authors determined myocardial and brain blood flows with radiolabeled microspheres, while CPP was defined as the aortic-to-right atrial pressure gradient during the relaxation phase of CPR. Each time the ITD was removed from the respiratory circuit, the CPP and vital organ perfusion decreased while perfusion pressures stabilized or increased when the valve was placed back in the circuit. A subsequent prospective, blinded study demonstrated a significantly higher end tidal CO₂ and systolic blood pressure when an active ITD was used^[42]. These results were further confirmed by an independent study (without the patent holder as one of the authors) which demonstrated that the ITD doubled blood flow to the heart when compared with standard CPR^[43]. Table 1 shows changes in CPP values when ITD was added to CPR efforts.

In addition to an increase in hemodynamics, the beneficial effects of standard CPR plus an ITD can also be seen on survival and neurological function. A statistically significant increase in 24-h survival and neurological function was demonstrated when the ITD was used during standard CPR^[42]. One of eleven animals *vs* twelve of seventeen had completely normal neurological function when a sham *vs* an active ITD was used ($P < 0.05$). In addition, the ITD lowers intracranial pressure during the decompression phase similar to the mechanism of the “last gasp”, thereby reducing resistance to forward

Table 1 CPP values in diverse animal studies

First author	CPR method	CPP	↑ CPP (%)	P-values with ITD
Lurie <i>et al</i> ^[36]	ACD-CPR	21 ± 3.6	47.6	< 0.05
	ACD-CPR + ITD	31 ± 2.3		
Lurie <i>et al</i> ^[41]	S-CPR	14 ± 2	42.9	< 0.006
	S-CPR + ITD	20 ± 2		
Raedler <i>et al</i> ^[44]	S-CPR	15 ± 2	93.3	< 0.001
	ACD-CPR + ITD	29 ± 3		
Srinivasan <i>et al</i> ^[45]	S-CPR	17.4 ± 3	64.7	< 0.01
	ACD-CPR + ITD	28.3 ± 2		
Metzger <i>et al</i> ^[46]	S-CPR	22.4 ± 1.6	31.8	< 0.05
	ACD-CPR + ITD	29.5 ± 2.7		
Yannopoulos <i>et al</i> ^[47]	S-CPR	14 ± 3	128.6	< 0.01
	ACD-CPR + ITD	32 ± 5		

CPP: Coronary perfusion pressure; ITD: Impedance threshold device; CPR: Cardiopulmonary resuscitation; ACD-CPR: Active compression decompression cardiopulmonary resuscitation; S-CPR: Standard cardiopulmonary resuscitation.

blood flow to the brain^[48]. Moreover, Yannopoulos *et al*^[49] reported a significant and dose-dependent decrease in intracranial pressure both at baseline and after a successful resuscitation with the use of an ITD compared with spontaneous breathing.

Active compression decompression CPR (ACD-CPR) combined with an ITD

Various studies combined ITD with an automated device that actively compresses and then decompresses the chest with a suction cup attached to the anterior chest wall.

The addition of an ITD during ACD-CPR in a porcine model of CA resulted in a marked enhancement of vital organ blood flow and coronary perfusion pressure (Table 1) and a decrease in the total energy required for effective defibrillation^[36]. A remarkable increase in perfusion pressures and, subsequently, vital organ blood flow above the threshold that rendered successful defibrillation was also demonstrated by Voelckel *et al*^[50]. The increase in perfusion pressures and vital organ blood flow occurred when global ischemia reached a point that renders many CPR interventions barely effective. With the use of the ITD, six of seven animals had ROSC after a total of 26 min.

During the very special situation of hypothermic CA, ACD-CPR together with an ITD improved common carotid blood flow compared with standard CPR alone (67 ± 13 mL/min *vs* 26 ± 5 mL/min, respectively, $P < 0.025$)^[44]. The beneficial effects of the combination of ACD-CPR with an ITD were also seen on cerebral metabolism. Using the technique of microdialysis, researchers measured the changes in brain biochemistry during and after hypothermic cardiopulmonary arrest. Apparently, ITD improved the lactate-pyruvate ratio and glucose metabolism in comparison to standard CPR^[51]. These findings are a potent marker of a better metabolic status with less anaerobic glycolysis.

Table 2 ROSC in diverse animal and human studies

First author	CPR method	ROSC (%)	↑ (%) with ITD	P-values
Animal studies				
Lurie <i>et al</i> ^[36]	ACD-CPR	77.8	28.5	0.18
	ACD-CPR + ITD	100		
Lurie <i>et al</i> ^[41]	S-CPR	18.2	199.5	< 0.05
	S-CPR+ITD	54.5		
Raedler <i>et al</i> ^[44]	S-CPR	0		0.06
	ACD-CPR + ITD	42.9		
Srinivasan <i>et al</i> ^[45]	S-CPR	37.5	166.7	< 0.05
	ACD-CPR + ITD	100		
Matsuura <i>et al</i> ^[52]	S-CPR	83.3	20.0	-
	S-CPR + ITD	100		
Human studies				
Vartanian <i>et al</i> ^[53]	S-CPR	45.0	31.1	0.03
	S-CPR + ITD	59.0		
Aufderheide <i>et al</i> ^[54]	S-CPR	33.8	12.1	0.022
	S-CPR + ITD	37.9		
Plaisance <i>et al</i> ^[55]	ACD-CPR	20.0	82.0	0.4
	ACD-CPR + ITD	36.4		
Wolcke <i>et al</i> ^[56]	S-CPR	37.0	48.6	0.016
	ACD-CPR + ITD	55.0		

ROSC: Return of spontaneous circulation.

In addition, it has been demonstrated that after ROSC a rapid ice-cold saline infusion combined with ACD-CPR plus an ITD induces cerebral hypothermia more rapidly than standard CPR^[45]. Table 2 shows the improvement of ROSC when ITD was implemented in CPR efforts.

CLINICAL STUDIES

The results of human clinical trials seem to reflect the data seen in animal models.

Standard CPR combined with an ITD

Systolic blood pressure was doubled when the ITD was used in 10 patients with out-of-hospital CA compared with similar patients treated with standard CPR^[57]. Mean systolic blood pressure increased from 45 to 85 mmHg ($P < 0.001$) when a sham *vs* active ITD was used^[57].

Adoption of the 2005 CPR guidelines and ITD resulted in a 75% increase in initial arrest survival rates and a 62% increase in survival to hospital discharge rates^[58]. In a concurrent, randomized, blinded clinical trial focused on ICU admission rates, survival rates were higher in patients treated with standard CPR plus an ITD, especially in those who presented with pulseless electrical activity (over 100% increase in short-term survival)^[59].

Moreover, adding an ITD to standard resuscitation care improved overall short-term survival by 50% and tripled survival in patients with traditionally the poorest outcomes, those with asystole^[60]. No device-related adverse effects were observed.

Implementation of the 2005 AHA CPR guidelines together with an ITD resulted in a marked increase in

Table 3 Patients discharged from hospitals with intact neurological function

First author	CPR method	Normal neurological function	P-values
Vartanian <i>et al</i> ^[53]	S-CPR	4/104	NS
	S-CPR + ITD	0/143	
Plaisance <i>et al</i> ^[55]	ACD-CPR	1/10	0.9
	ACD-CPR + ITD	1/11	
Wolcke <i>et al</i> ^[56]	S-CPR	4/75	0.4
	ACD-CPR + ITD	8/82	
Plaisance <i>et al</i> ^[62]	ACD-CPR	1/8	0.1
	ACD-CPR + ITD	6/10	

NS: Non significant.

Table 4 Hospital discharge rates in various human studies

First author	CPR method	Hospital discharge rates (%)	↑ (%) with ITD	P-values
Thigpen <i>et al</i> ^[58]	S-CPR	17.2	62	0.034
	S-CPR + ITD	27.9		
Davis <i>et al</i> ^[61]	S-CPR	20.7	73	< 0.001
	S-CPR + ITD	35.8		
Aufderheide <i>et al</i> ^[54]	S-CPR	7.9	98	< 0.001
	S-CPR + ITD	15.7		
Lurie <i>et al</i> ^[63]	S-CPR	9.3	83	0.0373
	S-CPR + ITD	17		

in-hospital discharge rates of more than 70% when compared with historical controls in two large community hospitals^[61].

The highest overall resuscitation rates in its 30-year history were observed when ITD was used by an EMS. The benefit was observed regardless of presenting rhythm. ROSC rates increased by 29% and neurologically intact discharge rates improved by > 50%^[53]. Table 2 shows ROSC values in diverse studies when ITD was used in the respiratory circuit, while Table 3 shows hospital discharge of patients with intact neurological function.

Adoption of the ITD by 7 EMS systems who treated 893 CA victims with standard CPR, resulted in only a > 10% increase in ROSC rates but a doubling of hospital discharge rates, from 7.9% to 15.7% ($P < 0.001$)^[54]. Table 4 shows hospital discharge rates in diverse studies.

ACD-CPR combined with an ITD

A study performed in prehospital mobile intensive care units in France was designed to evaluate acute hemodynamic parameters in non traumatic patients with prolonged CA treated with ACD-CPR alone or ACD-CPR plus an ITD^[55]. The study demonstrated that use of an ITD during CPR further optimizes mechanical measures associated with ACD-CPR by increasing venous return and CPP. Diastolic arterial pressures and CPP were 70% higher than those achieved with ACD-CPR alone. In addition PETCO₂ levels were significantly higher when ITD was used^[55].

The hemodynamic benefit observed in a previous

study was translated to a direct increase in survival rates and improved neurological function.

A prehospital clinical trial in Germany found significantly improved ROSC, 1 and 24-h survival rates when the combination of ACD-CPR and an ITD was compared with standard CPR alone (55% *vs* 37%, $P = 0.016$, 51% *vs* 32%, $P = 0.006$, 37% *vs* 22%, $P = 0.033$, respectively)^[56]. One-hour and twenty four-hour survival rates in witnessed arrests were 55% and 41% with ACD CPR plus an ITD *vs* 33% and 23% in control subjects ($P = 0.011$ and 0.019), respectively. One-hour and twenty four-hour survival rates in patients with a witnessed arrest in ventricular fibrillation were 68% and 58% after ACD-CPR with an ITD *vs* 27% and 23% after standard CPR ($P = 0.002$ and 0.009 , respectively). Survivors of this study treated with ACD-CPR plus an ITD had a marked improvement in their brain function at the time of hospital discharge^[56].

Additional support for these findings was provided by another study which demonstrated that the combination of ACD-CPR and ITD in 400 patients with out-of-hospital CA resulted in a doubling of 24-h survival^[62]. In that study, patients were treated with either a sham or an active ITD. The neurologic function in the survivors was significantly better at hospital discharge in patients treated with the ITD.

A meta-analysis that included 833 patients from five high quality randomized studies concluded that the ITD consistently and significantly improved ROSC (46% for ITD group *vs* 36% for control, $P = 0.002$), early survival (32% *vs* 22%, $P = 0.0009$) and favorable neurologic outcome (13% *vs* 6%, $P = 0.004$)^[64].

CONTROVERSIAL ITD STUDIES

An independent blinded study in a porcine model of CA tried to assess the effect of the ITD on CPP and passive ventilation (PaO₂ and PaCO₂) during standard CPR and its impact on the ROSC and short-term survival. In contrast to previous studies, use of the active ITD had no significant impact on CPP, passive ventilation, or outcomes compared to the sham device^[65].

Furthermore, in a study by Menegazzi *et al*^[66] use of the ITD during standard CPR did not improve CPP compared to standard CPR alone and also resulted in significantly lower ROSC and short term survival.

Finally, in a porcine model with a beating heart, use of an ITD combined with apnoeic oxygenation and without active ventilation during chest compressions resulted in hypoxemia due to transiently impaired lung function^[67]. This study raised concerns from other investigators who claimed that Herff *et al*^[67] misapplied the device and used a study design irrelevant to the recommended clinical use of the ITD, as an ITD is designed for patients in CA who are being actively ventilated^[68].

CONCLUSION

Taken together, these observations suggest that enhance-

ment of negative intrathoracic pressure during the decompression phase of CPR is associated with a marked cardiac preload. It is clear that priming the pump prior to cardiac defibrillation with the use of an ITD increases the chances for successful defibrillation. The hemodynamic benefits of the ITD during standard and ACD-CPR are striking in animals and in patients. Use of the ventilation timing lights on an ITD reduces the frequent, lethal rescuer error of hyperventilation. The ease of use of this device, its ability to be incorporated into a mask and other airway devices, the absence of device-related adverse effects and few requirements in additional training, suggest that ITD may be a favorable new device for improving CPR efficiency.

ITD offers new hope for survival in patients experiencing CA. Improved vital organ perfusion during CPR with the ITD is an important advance in resuscitation but it should be always kept in mind that by itself the ITD is not a panacea. It should be coupled with excellent preresuscitation and postresuscitation care to achieve better outcomes.

Since the literature is still short of studies with clinically meaningful outcomes such as neurological outcome and long term survival, further evidence is still needed.

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Perfusionist strategies for blood conservation in pediatric cardiac surgery

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Abstract

There is increasing concern about the safety of homologous blood transfusion during cardiac surgery, and a restrictive transfusion practice is associated with improved outcome. Transfusion-free pediatric cardiac surgery is unrealistic for the vast majority of procedures in neonates or small infants; however, considerable progress has been made by using techniques that decrease the need for homologous blood products or even allow bloodless surgery in older infants and children. These techniques involve a decrease in prime volume by downsizing the bypass circuit with the help of vacuum-assisted venous drainage, microplegia, autologous blood predonation with or without infusion of recombinant (erythropoietin), cell salvaging, ultrafiltration and retrograde autologous priming. The three major techniques which are simple, safe, efficient, and cost-effective are: a prime volume as small as possible, cardioplegia with negligible hydric balance and circuit residual blood salvaged without any alteration. Furthermore, these three techniques can be used for all the patients, including emergencies and small babies. In every pediatric surgical unit, a strategy to decrease or avoid blood bank transfusion must be implemented. A strategy to minimize transfusion requirement requires a combined effort involving the entire surgical team with pre-, peri-, and postoperative planning and management.

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INTRODUCTION

Blood transfusion is life-saving therapy but there is increasing concern regarding the drawbacks of homologous blood perfusion during pediatric heart surgery. Several studies suggested that a restrictive transfusion practice improved outcome by decreasing morbidity and mortality. Viral transmission is a historical risk, but stored blood bank transfusion generates inflammation, increases the risk of organ dysfunction and affects pulmonary and right ventricular function^[1,2]. Immunomodulation with down-regulation of cellular immune function increases the risk of nosocomial infections^[3,4]. Furthermore, transfusion of older blood raises the incidence of serious complications and increases time to ventilation^[5-7]. Transfusion related acute lung injury, an uncommon but probably underestimated complication, is one of the leading causes of transfusion-related mor-

bidity and mortality^[8,9]. Its incidence is estimated to be 1 out of 5000 units of packed red blood cells, 1 out of 2000 plasma-containing components and 1 out of 400 units of platelet concentrates^[10]. Its immunological origin *via* an antibody-mediated reaction is strongly suspected. Graft *vs* host disease is a very rare but usually fatal complication that also demonstrates the conjunction of immunity and blood transfusion^[11,12]. All these negative side effects of homologous blood transfusion are currently more obvious because of the dramatic decrease in post-operative mortality and morbidity. A reevaluation of our transfusion practice is needed to examine the risk/benefit ratio of blood transfusion during modern pediatric open-heart surgery.

There are several approaches to blood conservation among which reduction of prime volume *via* miniaturization of the bypass circuit and microplegia are the major factors^[13-17].

Ultimately, blood conservation is a perfect example of team work; everyone must be motivated to optimize reduction in blood use^[18].

The goal of this review is to analyze the different approaches to blood conservation and to describe their clinical advantages with regard to patient outcome.

BLOOD CONSERVATION STRATEGIES

Reduction in prime volume using a reduced bypass circuit

Reduction in prime volume is a major factor in blood conservation. If we assume a blood volume of about 80 mL/kg for neonates, the blood volume of a 3 kg baby is 240 mL. For this category of patients the prime volume is often equivalent or even higher than their blood volume. Therefore asanguineous priming is unrealistic except for rare cases with a high hematocrit level prior to surgery^[18]. However, it is possible to downsize the bypass circuit and thus decrease the prime volume. The two smallest membrane oxygenators dedicated to neonatal perfusion are the Kids D 100 (Sorin-Group, Mirandola, Italy), the prime volume of which is 31 mL, and the Baby FX (Terumo, Tokyo, Japan) with a built-in arterial filter and a prime volume of 43 mL. In our experience, the maximal blood flow with the Kids D 100 is 1 L/min, and the maximal blood flow with the Baby FX is 1.5 L/min. Downsizing of the circuit not only includes a decrease in the length and internal diameter of the arterial, venous, and suction lines but also elimination of any non-essential components. A prime volume of 172 mL is obtained with a bypass circuit composed of a 1/8 inch arterial line and a 3/16 inch venous line, which are connected to either a Baby RX-5 Terumo oxygenator or to a Lilliput 1 Sorin oxygenator. This circuit, without an arterial filter, is used for patients up to 5.1 kg^[13]. A bypass circuit with 3/16 inch tubing connected to a Kids D 100 oxygenator and a Sorin arterial filter D 130 allows reduction of the prime volume to 110 mL and its use is described for patients up to 4.1 kg^[19]. An original circuit

is composed of a distant roller pump and remote control unit (Tonokura Compo III; Tonokura Medical Inc., Tokyo, Japan). The roller pump is very near the patient so that the lengths of the venous and arterial lines are minimal. Tubing internal diameter is 3/16 inch for the pump boot and 5/32 inch for the lines. The prime volume of this circuit that includes an arterial filter is 140 mL^[16]. With the same pump another circuit is composed of a Safe-micro oxygenator (Polystan, Vaerloose, Denmark) connected to 5/32 inch internal diameter tubing. This circuit has no arterial filter but includes a hemofilter. The minimal prime volume is 130 mL^[20].

Our group currently uses a bypass circuit with a prime volume of 100 mL including priming of the microplegia circuit. The membrane oxygenator is a Kids D 100 from Sorin-Group; the arterial and venous lines have an internal diameter of 4 mm, and there is no arterial filter or hemofilter. This circuit is, at the present time, used for blood flow up to 0.6 L/min but the maximal flow is still to be determined.

It is interesting to note the following observations: (1) the internal diameter of the arterial line may be decreased to 1/8 inch for patient weight up to 5 kg, or to 5/32 inch (which is about 4 mm) for patients up to 7 kg; (2) the arterial filter, usually known as a safety device, is no longer considered essential; and (3) the hemofilter is not a constant component of the bypass circuit (filling of the filter and its connective tubing increased prime volume, and thus hemodilution).

Another positive side effect of the miniaturized circuit is reduced blood contact with the surface of the cardiopulmonary bypass circuit; this contact is thought to activate the systemic inflammatory response.

Vacuum-assisted venous return

Vacuum-assisted venous return is helpful to further decrease prime volume. Such assisted venous drainage allows us to decrease declivity of the membrane oxygenator, and thus, to significantly decrease the length of the venous, arterial and suction lines. This technique was first developed in adult surgery and was considered a powerful system to decrease hemodilution during cardiopulmonary bypass^[21]. Furthermore, vacuum-optimized venous return flow, and full support blood flow rates can be achieved through cannulae that demonstrate limited flow capacity under siphon drainage conditions. We currently use vacuum-assisted venous drainage, and we have lifted the oxygenator, so that the top of the cardiotomy reservoir is at the level of the patient's right atrium^[22]. In this position gravity-siphon venous drainage is limited and, thus, insufficient to perform full-flow bypass. In cases of technical failure in the wall vacuum source, it is essential to find another way of generating negative pressure in the cardiotomy reservoir. A negative pressure, with values equivalent to those obtained by the use of vacuum wall source, can be achieved through a roller pump sucking air out of a closed cardiotomy reservoir^[23].

An increase in gaseous microemboli is a complica-

tion related to vacuum-assisted venous drainage. However, this drawback is avoidable by adhering to specific parameters^[24,25]. If the maximal value of the vacuum remains under -40 mmHg, the level of embolic activity is equivalent to that seen during gravity-siphon venous drainage^[26]. When using vacuum-assisted venous drainage, a pressure relief valve is an essential component of the circuit. This valve is built-in in the Kids D 100 oxygenator but must be added with the Baby FX membrane. The valve opens whenever the cardiectomy reservoir pressure increases above 5 mmHg or decreases below -80 mmHg. Before the use of this safety device, overpressurization of the cardiectomy reservoir was possible, with reverse flow in the venous line and left sided gas embolism through an atrial septal defect^[27]. Continuous monitoring of the negative pressure in the cardiectomy reservoir is simple and important to increase the safety of the technique.

The hypothesis of an increase in hemolysis during use of the vacuum was ruled out by several investigators^[28,29]. Vacuum-assisted venous return is a technique, without any obvious drawbacks, that is used by several pediatric centers with consistent ability to reduce homologous blood transfusion^[19, 30-32].

Microplegia or miniplegia

The original composition of blood cardioplegia described by Buckberg was a mixture of 4 parts blood added to 1 part crystalloid; this has become the standard for cold blood cardioplegia^[33]. Alteration of this composition was proposed by several authors when warm, or at least tepid, and blood cardioplegia was adopted^[34,35] because the only rationale for dilution was to decrease high blood viscosity associated with hypothermia. Furthermore, at that time cardioplegia was retrograde and performed continuously through the coronary sinus. The risk of fluid overload and of clotting factor dilution was real with standard blood cardioplegia. Microplegia was then also used for intermittent warm blood cardioplegia^[36-38]. The technique for continuous or discontinuous microplegia injection is identical. Blood is diverted from the arterial line or from a specific built-in port of the oxygenator through an occlusive roller pump. Downstream of the roller pump, the arresting agent is added *via* a syringe pump. In our experience, the result is a mixture of 60 parts of oxygenated blood to one part of crystalloid cardioplegia solution^[39]. With this mixing ratio of 60, the rotor speed of the occlusive pump driving blood in mL per min is equivalent to the speed of the electrical syringe adding arresting agent in mL per hour.

The theoretical advantages of non-diluted cardioplegia are as follows: (1) a higher myocardial oxygen supply because of a higher hemoglobin level and a rightward shift of the oxyhemoglobin dissociation curve; (2) a negligible fluid balance of the cardioplegia (the volume of blood diverted from the circuit is sucked from the coronary sinus to the cardiectomy reservoir so that the balance is limited to a few milliliters of crystalloid-ar-

resting agent); (3) a decreased tendency for tissue edema with non-diluted *vs* diluted cardioplegia demonstrated in experimental data^[40]; and (4) cost-effectiveness when compared to the standard cardioplegia technique.

In clinical studies there are either similar results for microplegia and standard blood cardioplegia with regards to in-hospital morbidity and mortality, or better results for microplegia *vs* standard cardioplegia with regard to myocardial protection^[36-38]. However, in all these studies the benefit to hydric balance of microplegia *vs* standard cardioplegia is observed. When using standard cardioplegia with a blood to crystalloid ratio of 4/1, cardioplegia is sucked into the cardiectomy reservoir, dilution of the circulating blood increases during each cardioplegia injection. The dilution is significant during complex procedures that require prolonged cross-clamp times. When standard cardioplegia is wasted, blood is also wasted; and crystalloid or colloid must be added to restore the level in the cardiectomy reservoir.

Autologous blood predonation

Preoperative blood donation in pediatric cardiac surgery is not common practice except in some countries such as Japan for children between 3 and 10 years old and with a minimum weight of 12 to 13 kg^[41-44]. The technique is said to be safe and efficient in decreasing homologous blood transfusion. A study was performed in 37 patients ranging from 3 to 9 years old and weighing from 13 to 20 kg; multiple donations were performed over a 2 mo period. The result was a blood storage volume of 48 ± 17 mL/kg such that no homologous blood transfusion were used in the preoperative donation group *vs* 80% in the control group^[44]. More recently, 23 children with simple cardiopathies were included in a preoperative blood donation program and compared to a control group of 27 age- and weight-matched children. Their age varied from 6 mo to 5 years, and their body weight ranged from 6.1 to 14 kg. In the donation group, two donations of 10 mL/kg were performed *via* the femoral vein under mild general anesthesia about 3 wk and 2 wk before surgery. The two groups had similar hemoglobin levels before, during and after surgery, however, the incidence of homologous blood transfusion was 44.4% in the control group compared with 4.3% in the donation group^[45]. One important factor is the preoperative level of hemoglobin as there is a risk of proceeding to surgery with a lower hemoglobin level. To overcome this risk, concomitant treatment with erythropoietin has been proposed. The best results were obtained when a higher dosage of erythropoietin (300 units/kg) was injected 1 wk before the first donation and 300 units/kg at each of the two subsequent donations. With this protocol the decrease in hematocrit was minimal, from 39.0% \pm 0.6% before donation to 37.5% \pm 0.5% before surgery^[46]. Another study was performed on 39 patients with well-tolerated simple cardiopathies (atrial or ventricular septal defect), pretreatment hemoglobin levels of between 10 to 14 g/dL. The group treated

with erythropoietin received 100 units/kg three times a week for 3 wk and 100 units/kg the day of surgery to a total dose of 1000 units/kg. Despite a moderate decrease in hemoglobin during the autologous blood donation period in the treated group, there were less blood bank transfusions from 61.5% in the control group to 7.7% in the treated group^[47]. To avoid the delay necessary for preoperative blood donation and the constraints of the technique, a single subcutaneous dose of erythropoietin given one has been studied. However, this therapeutic approach failed to exhibit any significant reduction in homologous blood transfusion^[48]. There are many limitations to preoperative autologous blood donation. The technique is not suitable for neonatal surgery or emergencies. A weight less than 5 kg, complex cardiopathies and low hemoglobin levels are contraindications. Furthermore, the technique is inconvenient for children and families. It is also time consuming for medical staff and expensive for hospitals, especially erythropoietin is used. The benefits of preoperative autologous blood donation are real but further work is needed: (1) to compare donation to other ways of decreasing homologous blood transfusion and (2) to find the correct indication for preoperative blood donation and/or preoperative erythropoietin therapy.

Cell-salvage techniques

Cell salvage techniques scavenge blood loss. There are two main techniques of cell-salvage: the blood is either collected and reinjected without any treatment (non-wash technique), or the blood is treated and anticoagulated, washed and centrifuged in a cell-saver machine to obtain a concentrate of red blood cells. The washing technique is said to remove debris from shed blood thus reducing the risk of cerebral thromboembolism and improving neurological outcome. Washing also removes platelets, coagulation factors and other plasma proteins leading to coagulopathy, and an increased risk of organ failure and of systemic inflammatory response^[49-53]. However, the safety of the cell salvage technique has been shown in multiple studies^[54-56]. The benefits of cell salvage in reducing allogeneic blood transfusion is controversial. A meta-analysis failed to find any significant benefit from cell salvage in cardiac surgery^[57], while other studies demonstrated a significant reduction in blood transfusion with washed salvaged blood^[55-58]. One of the major limitations of washing blood in pediatric surgery is that it is time-consuming during which the blood is unavailable to the patient. Recent progress has been made with the introduction of a small-volume centrifugal bowl dedicated to pediatric patients. The HaemoLite 2 plus device with a 100 mL centrifugal bowl (Haemonetics, Bothwell, UK) was tested in a pediatric center on a group of 59 patients and compared to a control group of 63 patients. All the patients had undergone first-time cardiac surgery. The control group had cell-salvage limited to residual volume of the circuit while the studied group also underwent intraoperative cell salvage. Transfusion of allogeneic red blood cells in the ICU was used in 59% of

patients in the control group and only 27% of patients in the studied group. However, for 83% of the children with a body weight less than 10 kg, blood collected during surgery was not sufficient to fill the 100 mL bowl. Consequently, salvage blood was not treated with the cell-saver device and not available for transfusion. The difference in cell saving volume product was only 31 mL, from 152 ± 57 mL in the control group to 183 ± 56 mL in the studied group. Furthermore, the cost of shed blood collection was higher than the savings from reductions in the number of banked blood transfusions^[59].

Obviously, the results of the cell-saver technique are widely influenced by surgical hemostasis by the motivation for blood preservation. Another component influencing the results of cell salvage is the use of residual volume in the circuit after coming off cardiopulmonary bypass. Some centers add this residual blood to the cell-saver for washing while transfuse it directly into the patient. We advocate collection of residual blood from the circuit without any further treatment. The quality of this blood is exactly the same as the quality of the patient's blood at the time of discontinuation of cardiopulmonary bypass. We pool the residual blood with the remaining blood bank products, if any, in a bag. This blood is used during the post-bypass period when necessary. This blood contains coagulation factors that are otherwise removed during cell-saver treatment. It also contains heparin which can be removed by adding additional protamine as needed. This policy has proven to be safe, efficient, simple and less expensive than cell salvage^[13].

Ultrafiltration

Reductions in blood transfusion is described following ultrafiltration. However, it is unclear whether this benefit is due to the volume of fluid removed from the circulating bypass blood *vs* the modified ultrafiltration^[60-63]. There are conflicting results about the different ultrafiltration techniques, because in neonatal surgery, removal of fluid from a miniaturized circuit during cardiopulmonary bypass, corresponding to conventional ultrafiltration, is difficult and inconsistent when fluid replacement is needed to maintain adequate reservoir level^[64]. Modified ultrafiltration is performed after discontinuation of cardiopulmonary bypass to reduce hemodilution and decrease tissue edema. In most studies, modified ultrafiltration has improved dilutional coagulopathy and reduced blood transfusion requirements^[65]. However, the technique also has drawbacks, and 82% of the centers using modified ultrafiltration experienced complications related to the technique^[66]. Modified ultrafiltration may be obsolete as there are strategies to avoid or at least minimize hemodilution^[15]. In several centers where miniaturized bypass circuits have been implemented, ultrafiltration is no longer used^[13-15,18,19].

Maneuver of retrograde autologous priming

Retrograde autologous priming consists of total or partial

replacement of the crystalloid prime by using the patient's blood being drained from the arterial and venous lines. During this drainage, the bloodless prime is redirected to a separate reservoir. This is a well established way to decrease autologous blood transfusion in adult cardiac surgery^[67,68]. This strategy is very uncommon in pediatric cardiac surgery, but it could be part of a bloodless surgical program^[69]. The technique is dependent on the size of the patient and the individual hemodynamic tolerance of blood withdrawal.

CONCLUSION

There are several ways to decrease the number of blood bank transfusions or even perform donor blood-free pediatric cardiac surgery. The effects of the different techniques are not always cumulative. The major techniques are as follows: (1) downsizing of the bypass circuit which decreases dilution and dilutional coagulopathy; (2) vacuum-assisted venous drainage when its use is associated with further reduction of the bypass circuit prime; (3) microplegia; and (4) cell salvage of the residual blood from the circuit without treatment. These four techniques are simple, inexpensive, safe and efficient in all patients regardless of age or weight. The other techniques (autologous blood predonation, cell-salvage, ultrafiltration, retrograde autologous priming) could be used in combination with the major techniques, with some benefit, in selective cases.

However, the success of any program of blood conservation is not only linked to the perfusionist's experience but also depends on the motivation of all the actors involved in the patient's care before, during and after surgery.

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Current advances in the understanding of coronary vasospasm

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Abstract

Recent years have witnessed progress in our understanding of coronary vasospasm (CVS). It is evident that this is not only an East Asian but also a global disease associated with significant symptoms and possible lethal sequelae for afflicted individuals. A correct diagnosis depends on the understanding of pathogenesis and symptomatology of CVS. With the correct diagnosis, we can manage CVS patients effectively and promptly, providing optimal patient safety. Advances in our understanding of interactions between inflammation, endothelium, and smooth muscle cells have led to substantial progress in understanding the pathogenesis of symptoms in CVS and have provided some insights into the basic etiology of this disorder in some patient subpopulations. We look forward to a time when therapy will address pathophysiology and perhaps, even the primary etiology.

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Key words: Coronary vasospasm; Endothelial nitric oxide synthase; Inflammation; Nitric oxide; Rho-kinase

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INTRODUCTION

Coronary vasospasm (CVS) with transient ST-segment elevation can occur in diseased coronary arteries as Prinzmetal's variant angina^[1]; it may also occur in angiographically normal coronary arteries as so-called 'variant of the variant' angina^[2]. Subsequently, many investigators found that most CVS are associated with ST-segment depression rather than ST-segment elevation on electrocardiography (ECG)^[3-5]. Therefore, variant angina is only one aspect of the spectrum of coronary vasospastic myocardial ischemia^[6]. CVS plays an important role in the pathogenesis not only of variant angina, but also of ischemic heart disease, including effort angina, unstable angina, acute myocardial infarction, and sudden death^[7-11]. Therefore, angina caused by CVS is now usually called 'coronary vasospastic angina'. The name 'variant angina' is less often used and is usually denoted as angina with transient ST-segment elevation.

CASE PRESENTATION

A 67-year-old man was admitted at midnight (0:30 am) to the emergency department due to sudden onset ischemic chest pain associated with cold sweating and palpitation. He was a heavy smoker who had experienced several of these episodes during the past 15 years in which most episodes occurred in the early morning hours. The baseline ECG (Figure 1A) showed no evidence of

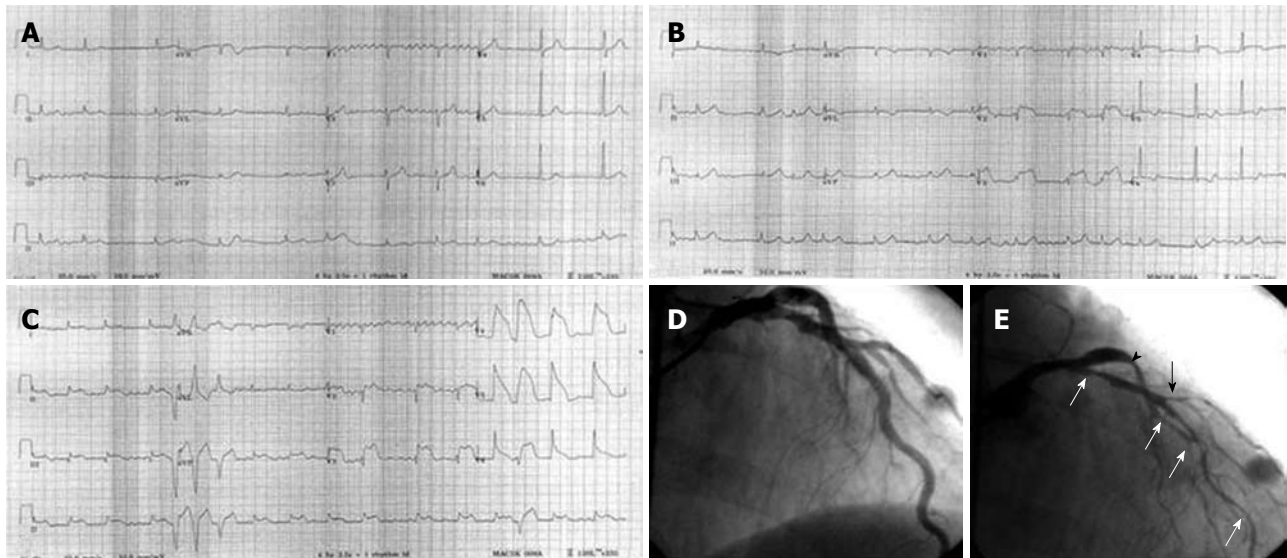


Figure 1 Baseline electrocardiography (ECG) of a patient with variant angina. A: The ECG showed no evidence of myocardial ischemia on admission to the emergency department; B: A few hours later, the follow-up ECG, due to chest pain, showed ST-segment elevation in the V₂₋₄ leads. C: During the following days, serial ECGs due to chest pain showed dynamic ST-segment elevation in the anterior and inferior leads. D: The patient's ECG was normal when he was not having chest pain. Baseline coronary angiography showed no evidence of significant fixed coronary artery stenosis; E: Diffuse spasm in the proximal to distal portion (white arrows) and diagonal branch (black arrow) of the left anterior descending artery and in the proximal portion of the left circumflex artery (arrowhead) were noted following intracoronary methylethylergonovine administration.

myocardial ischemia on admission to the emergency department. A few hours later, the follow-up ECG due to recurrent chest pain (Figure 1B) showed ST-segment elevation in the V₂₋₄ leads. In the following days, serial ECGs due to chest pain showed dynamic ST-segment elevation (Figure 1C) in the anterolateral and inferior leads associated with multiform premature ventricular contractions. Cardiac troponin I was normal in two successive tests 6 h apart. The high-sensitivity C-reactive protein was also normal (0.65 mg/L). Baseline coronary angiography during admission showed no evidence of significant fixed coronary artery stenosis (Figure 1D). Diffuse spasm in the proximal to distal portion (white arrows) and diagonal branch (black arrow) of the left anterior descending artery and in the proximal portion of the left circumflex artery (arrowhead) were noted following intracoronary methylethylergonovine administration (Figure 1E). The diagnosis of coronary vasospastic angina was made. The patient responded well to two long-acting calcium antagonists (nifedipine and verapamil) and nicorandil. He had an uneventful follow-up period of 2 years.

DIAGNOSIS OF CVS: MOST CVS ARE ASSOCIATED WITH ST-SEGMENT DEPRESSION

The diagnosis of CVS is not necessarily easy. In contrast to stable effort angina, which is reproducibly induced by exercise testing, CVS is usually not induced by exercise, particularly in the afternoon; it occurs usually at rest, particularly from midnight to early morning.

The attack is transient, often lasts only a few minutes, and is unpredictable. Thus, ambulatory monitoring of ECG is important to detect the attack. However, even during ambulatory ECG monitoring, an attack may not be apparent, especially when attacks are infrequent. Furthermore, most CVS are associated with ST-segment depression rather than ST-segment elevation^[12]. Therefore, provocation tests for CVS were developed to make a diagnosis of CVS-related ischemic heart disease. An important issue is the indication of provocation testing performed. The pharmacologic provocation testing of CVS is recommended in patients with recurrent episodes of apparent ischemic chest pain at rest who have normal or mildly abnormal coronary angiograms, with no clinical observations substantiating the diagnosis of variant angina, i.e. ST-segment elevation during pain^[13].

Several provocative tests for CVS are available. Of these, the ergonovine and acetylcholine tests are most commonly used. Ergonovine is an ergot alkaloid that stimulates both α -adrenergic and serotonergic receptors, and intracoronary administration of doses ranging from 10-80 μ g in total are most commonly used. Intracoronary nitroglycerin 50-200 μ g is administered subsequently if the luminal diameter is decreased more than 70% after intracoronary ergonovine, in association with clinical symptoms and/or electrocardiographic changes^[14]. There is no standard definition for a positive intracoronary provocation test. Yasue *et al*^[15] defined CVS as an abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia. With this definition, there are no limits to the degree of lumen reduction required to diagnose CVS, since ischemia must accompany

the changes in vessel size. The American College of Cardiology/American Heart Association guidelines for coronary angiography suggest that CVS is present when a reduction in lumen diameter of $> 50\%$ occurs during a provocative test^[13]. In early 1990, coronary provocation testing using methylergonovine was developed^[16]. The intracoronary route of administration of methylergonovine for provocation of CVS is safe, sensitive, and specific. This route is preferable in hypertensive patients and affords the opportunity to evaluate the left and right coronary circulations separately. Auch-Schwelk *et al*^[17] reported that the contractions to ergonovine are not dependent on nitric oxide release, but are synergistically augmented by thromboxane. However, methylergonovine causes similar effects on vascular smooth muscle, but contractions are inhibited by the release of nitric oxide from the endothelium.

Intracoronary acetylcholine administration in doses of 10-100 μg is also used for CVS provocation^[18]. The duration of the action of acetylcholine is very short and the induced CVS usually disappears spontaneously within 2-3 min, without the need for intracoronary nitroglycerin administration. Sinus node and conduction system inhibition is a major side effect of the acetylcholine test in which temporary pacing is needed, especially when intracoronary acetylcholine is administered into the right coronary artery. Acetylcholine provocation is also commonly used to assess coronary endothelial function as it stimulates the release of endothelium-derived nitric oxide with subsequent vasorelaxation of the vascular smooth muscle cells. However, with increasing doses of acetylcholine application, the vasoconstrictor effect on the vascular smooth cells may override the endothelial effect and a vasoconstrictor response may result. Thus, in the normal setting, there is an endothelium-induced coronary vasodilation in response to acetylcholine stimulation, while in the presence of a dysfunctional endothelium the vasoconstrictor effects of acetylcholine prevail and cause a vasoconstriction. Overall, it may be difficult to differentiate between coronary endothelial dysfunction and a CVS, unless the vasoconstrictor response is distinct or $> 50\%$ of the vessel diameter. The vasomotion can result in as much as a $< 50\%$ change in vessel diameter in patients without CVS^[19]. This can also be applied for the cold pressor test.

CVS can also be induced by hyperventilation, which causes respiratory alkalosis^[20]. Its sensitivity is 65% and the specificity is 100%. It may be safe when CVS is induced by hyperventilation. Nonetheless, it may be dangerous to use this method to induce multivessel CVS. Histamine, epinephrine, dopamine, dobutamine, serotonin, exercise in the morning, and the cold pressor test all induce CVS with a lower sensitivity than ergonovine or acetylcholine^[21].

Angiographically normal coronary arteries occur in 25% of patients with acute coronary syndrome^[4,5,10]. The CVS can be induced in 50%-60% of these patients^[5,10]. Since variant angina is a presentation of transient ST-

elevation acute coronary syndrome, the diagnosis and initial management procedures must adhere to the guidelines proposed by the American Heart Association in 2005^[22]. Initial general therapies for acute coronary syndrome include immediate oxygen therapy, continuous cardiac monitoring, establishment of intravenous access, and medications of aspirin, nitroglycerin, and/or morphine. Morphine is indicated only for refractory chest pain after nitroglycerin use. If a normalized ST-segment is noted after the above general therapies, a diagnosis of variant angina is most likely and reperfusion therapy is unnecessary. If ST-segment elevation persists, then reperfusion therapies are necessary, according to the facilities available in the emergency room.

The importance of the differential diagnosis between persistence and transience of elevated ST-segments lies in the follow-up ECG and patient monitoring. The next diagnostic step for transient ST-segment elevation is coronary angiography, as this is the only certain method to distinguish between patients who have severe fixed multivessel disease or only angiographically normal or near-normal coronary arteries. This differential diagnosis is important because the treatment strategies proposed for variant angina with severe, fixed multivessel disease (e.g. aspirin, clopidogrel, nitrates, angiotensin-converting enzyme inhibitor, and/or percutaneous coronary intervention) or only angiographically normal or near-normal coronary arteries (e.g. calcium antagonists and/or nitrates) are different. Because there are some patients with CVS who are refractory to the conventional medications and who may suffer from life-threatening arrhythmias^[10] or sudden death^[23], and because percutaneous coronary intervention is not the correct management for CVS^[24], it is important for every emergency room, ward doctor, and cardiologist to be alert to the presence of CVS, a type of dynamic coronary artery stenosis, which may be silent and lethal.

In 1991, Dote *et al*^[25] first reported 5 cases of multivessel CVS and transient myocardial stunning. Thereafter, the term transient left ventricular apical ballooning or Takotsubo cardiomyopathy was used to describe transient myocardial stunning by many investigators. After recent investigations, Takotsubo cardiomyopathy is recognized as a form of myocardial stunning following a stressful event that is presumably induced by intense CVS^[26,27], microvascular dysfunction^[28,29], or a marked catecholamine response^[30,31]. Clinically, Takotsubo cardiomyopathy is characterized by (1) acute onset (usually following a stressful or emotional event, especially in older women); (2) variable severity of clinical (mainly, dyspnea and chest pain) and electrocardiographic manifestations of acute myocardial ischemia (typically involving territories larger than a single coronary branch); (3) mild cardiac enzyme elevation; (4) absence of obstructive, fixed coronary lesions on early angiographic images; (5) apical, anteroapical, and inferoapical hypo- or dyskinesia, with preserved basal-segment contractility, producing an ampulla-like systolic deformity of the left ventricular sil-

houette; (6) spontaneous resolution of all features in 1-4 wk, including normalized left ventricular function; and (7) a generally favorable late prognosis and rare recurrence rate. There are some different features between Takotsubo cardiomyopathy and CVS: (1) more postmenopausal female patients have Takotsubo cardiomyopathy; (2) older patients have Takotsubo cardiomyopathy; and (3) more daytime attacks of Takotsubo cardiomyopathy. Recent prospective studies suggest that the incidence of Takotsubo cardiomyopathy in acute coronary syndromes is 0%-2% on early coronary angiography^[32]. Another study in an Italian population revealed that 12% of female patients with suspected anterior acute myocardial infarction had Takotsubo cardiomyopathy^[33]. Although it is important to differentiate CVS from Takotsubo cardiomyopathy, there are some overlaps of these 2 entities. In a recent case series study of Takotsubo cardiomyopathy, the author described an experimental reproduction of transient apical ballooning in the catheterization laboratory during acetylcholine testing^[34]. The author suggested that coronary vasospastic angina is caused by localized, long-term neurohormonal dysfunction of one coronary artery, making patients susceptible to localized spastic episodes under transient influences of physiologic stimuli, such as emotions. On the other hand, onset of Takotsubo cardiomyopathy appears to represent the superimposition of transient diffuse endothelial dysfunction (probably lasting a finite period) and of an adrenergic surge episode. Persistent apical ballooning after the early stages appears to represent residual, secondary myocardial stunning. As a newly recognized disorder, much remains unknown about Takotsubo cardiomyopathy, especially its etiology. Many aspects are also puzzling. Nevertheless, delayed (5-30 d) acetylcholine testing accompanied by echocardiographic monitoring should be routinely pursued to identify the mechanism of Takotsubo cardiomyopathy, to better characterize individual prognoses, and to tailor treatments^[34].

NEW UNDERSTANDING OF THE MECHANISMS OF CVS

Autonomic system dysfunction

In the 1980s, researchers demonstrated that autonomic nervous system dysfunction was one of the possible mechanisms involved in the development of CVS^[18,35]. Pathologic findings of degeneration and fibrotic changes in the perivascular nerves of vasospastic coronary arteries support the hypothesis of autonomic nervous system dysfunction in CVS^[36].

Endothelial dysfunction, oxidative stress, and genetic susceptibility

In the 1990s, deficiency of nitric oxide activity due to endothelial dysfunction and oxidative stress were identified as other possible mechanisms for CVS^[37-40]. Plasma levels of vitamin E and another antioxidant were also found to be low in patients with CVS^[40,41]. Subsequently, Japanese

investigators showed that polymorphisms of Glu298Asp in exon 7 and T-786C in the 5'-flanking region of the endothelial nitric oxide synthase (eNOS) gene and paraoxonase gene Gln192Arg (Q192R) polymorphism were significantly associated with CVS^[42-44]. Paraoxonase I gene has an antioxidant effect and CVS occurs more often in cigarette smokers^[45]. Of CVS, endothelial function is impaired both in coronary and brachial arteries and is improved by vitamin C infusion in smokers^[46]. Cigarette smoke extract suppresses the acetylcholine-induced endothelium dependent vasorelaxation and the suppression is prevented by antioxidants in isolated arteries^[47,48]. Thus, cigarette smoking degrades nitric oxide through oxygen radicals. These findings suggest that decreased nitric oxide activity in CVS patients is partly due to increased nitric oxide degradation by oxygen radicals. However, eNOS polymorphisms are found in only one-third of CVS patients and therefore, other genes or factors may also be involved in the pathogenesis of CVS. Murase *et al*^[49] showed that while genetic risk and gene environment in both genders were involved with CVS, eNOS gene polymorphism was associated with CVS only in women^[50]. Type A personality, severe anxiety, and panic disorders were factors associated with CVS, even without significant obstructive coronary artery disease. Although the oxidized form of low-density lipoprotein impairs production of nitric oxide due to down-regulation of eNOS and the oxidative inactivation of nitric oxide by oxygen free radicals^[51,52], hypercholesterolemia is not a risk factor for CVS^[45,53]. Nakagawa *et al*^[12] found that CVS preferentially occurs at branch points and nonplaque sites, whereas the atherosclerotic lesion is predominantly localized at the nonbranch points of the curved proximal segments. This indicates that CVS may be a manifestation of coronary artery disease distinctly different from coronary atherosclerosis which is associated with hypercholesterolemia.

Smooth muscle hypercontraction

The classical pathway of vascular smooth muscle contraction through which stimuli induce myosin light chain phosphorylation is an increase of the intracellular Ca^{2+} concentration. However, Ca^{2+} -independent regulation also occurs through the inhibition of myosin light chain phosphatase, and the level of myosin light chain phosphorylation is determined by a balance between myosin light chain phosphorylation by myosin light chain kinase and dephosphorylation by myosin light chain phosphatase^[54]. Some investigators found that small GTPase RhoA and its downstream effector, ROCK/Rho-kinase, inhibit myosin light chain phosphatase resulting in accentuation of myosin light chain phosphorylation and Ca^{2+} sensitization in response to vasoconstrictor stimuli^[55]. In the late 1990s, researchers showed that RhoA/ROCK activity was enhanced in rat arteries with hypertension and vasospasm^[56,57]. Shimokawa *et al*^[58] and Kandabashi *et al*^[59] developed swine models of CVS and showed that ROCK activity is enhanced in coronary ar-

tery smooth muscle after wrapping the coronary artery with interleukin-1 beads. They subsequently showed that the ROCK inhibitor, fasudil, relieved CVS in humans^[60]. Thus, enhanced vascular smooth muscle contraction through the Rho/ROCK pathway plays an important role in the development of CVS. Recent studies show that decreased endothelial nitric oxide activity increases RhoA/ROCK activity in coronary arteries^[61,62]. Fluvastatin, which blocks the RhoA/ROCK pathway was also found to suppress CVS^[63]. These findings connect the activity of RhoA/ROCK to endothelial nitric oxide and are in agreement with the clinical observations that spastic arteries are supersensitive to both vasoconstrictor agonists and nitrates^[64].

Inflammation

In 1978, Lewis *et al*^[65] first reported a case of variant angina and localized pericarditis. They postulated that there was a link between inflammation and CVS. In the mid and late 2000s, we and others showed that chronic inflammation was associated with CVS, as evidenced by elevated peripheral blood monocyte counts, high-sensitivity C-reactive protein, interleukin-6, and adhesion molecules^[66-75]. Cigarette smoking, a major risk factor for CVS, is associated with low-grade inflammation^[76]. An interaction between smoking and high-sensitivity C-reactive protein was recently reported by our group^[77]. Based on several studies, inflammation exists in patients with CVS. However, the mechanism remains elusive.

Magnesium deficiency, insulin resistance, and K_{ATP} channel dysfunction

In the 1980s to 1990s, magnesium deficiency was also considered as a possible factor contributing to the genesis of CVS^[78,79]. Furthermore, it has been reported that infusion of magnesium reduced coronary spasm attacks in patients with CVS^[80,81]. The plausible mechanism might be the calcium channel blocking effect of magnesium ions at the level of vascular smooth muscle cells. Extracellular magnesium inhibits capacitative calcium ion entry in vascular smooth muscle cells^[82]. Magnesium-induced coronary dilatation may also be mediated *via* intracellular cyclic adenosine 3',5'-monophosphate. Previous studies have shown that adenosine 3',5'-monophosphate elevations contribute to coronary dilatation^[83]. Magnesium infusion may cause an increase in adenosine 3',5'-monophosphate within coronary smooth muscle cells, leading to the dilatation of coronary arteries^[84]. In 1995, Shinozaki *et al*^[85] found that insulin resistance associated with compensatory hyperinsulinemia is an independent factor for CVS. They postulated that hyperinsulinemia causes vascular endothelial dysfunction and CVS, and subsequently amplifies atherosclerotic lesion formation. However, CVS does not always precede obstructive atherosclerotic coronary artery disease. The mechanisms between insulin resistance and CVS have not been definitely defined. In 2006, Kakkar *et al*^[86] found that spontaneous CVS occurs in K_{ATP} mutant mice,

which arises from a smooth muscle-extrinsic process. They postulated that endothelial dysfunction with loss of K_{ATP} channels and decreased nitric oxide production and/or bioavailability promotes smooth muscle hypercontractility. Another possibility includes the sympathetic neurons, where opening of presynaptic K_{ATP} channels decreases norepinephrine release enhancing smooth muscle relaxation to dilate coronary arteries. A defect in these channels decreasing the threshold for norepinephrine release might be associated with CVS.

Summary

CVS provoked by ergonovine results in altered vascular muscle function rather than a disturbance in endothelial nitric oxide release^[17]. This is in line with clinical studies demonstrating endothelial dysfunction in many patients without evidence of CVS. Dysfunctional endothelium could play an additional role in the pathogenesis of CVS, because contractions due to the endogenous ligand serotonin are markedly augmented after inhibition of nitric oxide synthase^[17]. The interactions between the autonomic nervous system, inflammation, nitric oxide availability, eNOS regulation, Rho/ROCK activity of vascular smooth muscle cells, and K_{ATP} channels in smooth muscle cells provide some insights towards the basic etiology of this disorder in some subpopulations.

MANAGEMENT

In the event of an acute CVS attack, chest pain can usually be relieved by sublingual nitroglycerin. With occasional refractory CVS, intravenous or intracoronary administration of nitroglycerin may be necessary. Since the durations of action for nitroglycerin and nitrates are short, i.e. 1 h or less, the long-acting calcium antagonists are necessary to prevent recurrence. The effect of the calcium antagonists is often dramatic. Of particular importance, the calcium antagonist should be given before going to bed at night as CVS attacks usually occur from midnight into the early morning. It may require 2 calcium antagonists (dihydropyridine and non-dihydropyridine) to relieve CVS-related angina. Calcium antagonists should not be withdrawn even if symptomatic attacks occur rarely because of long-term spasticity-related silent myocardial ischemia^[45,87] and sudden death from life-threatening cardiac arrhythmias^[10]. Long-acting nitrates are also useful, but their potency is reduced by their tolerance. Combinations of different classes of calcium antagonists with nitrates may be necessary for patients with refractory CVS. β -blockers are not effective in suppressing CVS-related chest pain, especially in patients with angiographically normal or near-normal coronary arteries^[88]. Recent clinical research shows that magnesium^[81], statins^[63], antioxidants^[39,40], and the Rho-kinase inhibitor fasudil^[60] are also beneficial for the treatment of CVS. In addition to the use of effective anti-CVS medications, CVS inducers must be avoided. These inducers include cigarette smoking, catecholamines,

Table 1 Therapeutic strategies for CVS

Quit smoking	Obligatory
Long-acting Calcium antagonists	Use before going to bed at night
Long-acting Nitrates	Decreased potency by tolerance
Magnesium	Evidence by intravenous infusion
RhoA/ROCK inhibitor	Fasudil
Statins	Evidence by fluvastatin
Coronary bypass graft	Controversial
Implantable cardioverter defibrillator	For life-threatening ventricular arrhythmias

CVS: Coronary vasospasm.

muscarinic agonists, ergot alkaloids, prostaglandins, alcohol, emotional stress, and propranolol^[21].

The role of coronary intervention in patients with refractory CVS and organic stenosis is limited^[89]. In CVS patients who did not respond to conventional treatments, internal mammary artery revascularization with angiographically normal coronary arteries was reported^[90]. An implantable cardioverter defibrillator with aggressive medical therapy for CVS was reported to be effective in patients who had a previous syncopal event, documented ventricular tachycardia, or surviving out of hospital cardiac arrest^[91-93] (Table 1).

PROGNOSIS

The natural history of CVS-related ischemic heart disease is generally good as long as patients avoid cigarette smoking and have good compliance with adequate calcium antagonists therapy^[45,94-98]. Cardiac events are likely to occur during the first 3-6 mo. Patients without a stenosis of 70% or more have a 94% 1-year MI-free survival rate, while patients with multivessel atherosclerotic coronary artery disease and variant angina only have a 83% 1-year MI-free survival rate^[94]. A recurrent angina rate of 11% was noted in patients with CVS without significant fixed coronary artery disease during a 4-year follow-up period^[43]. Nonfatal acute myocardial infarction is a possible complication of variant angina with a incidence of 5%-10%^[94,99]. Seventy-five percent of nonfatal myocardial infarction occurs during the first 3 mo^[94]. The extent and severity of underlying fixed obstructive coronary artery disease is the prognostic factor which predicts survival within 3-6 mo after the diagnosis of CVS^[94]. Significant arrhythmic events during or following attacks of variant angina occur in 20%-50% of patients, among a large series of mostly untreated patients^[90]. The risk of sudden death for patients with coronary vasospastic angina is approximately 2% and is most common in patients with multivessel CVS and prior significant arrhythmias during angina occurrence^[99]. From another point of view, Wakabayashi *et al*^[100] tested consecutive Japanese patients for CVS 10-20 d after acute myocardial infarction treated by percutaneous coronary intervention. They found that provoked CVS occurs in 70% of infarct-related arteries and about 50% of noninfarct-related arteries. Provoked CVS was an independent predictor of adverse outcome.

CONCLUSION

Advances in our understanding of interactions between inflammation, the vascular endothelium, and smooth muscle cells have led to substantial progress in our understanding of CVS-pathogenesis and symptomatology, and have provided some insights towards the basic etiology of this disorder in some patient subpopulations. The absence of significant obstructive coronary artery disease should not lead the physician to conclude that the patient does not have ischemic heart disease. Since most patients with CVS present with ST-segment depression rather than ST-segment elevation, a high index of suspicion for CVS-related ischemic chest pain is important, because the treatment of choice varies accordingly. Many young cardiologists are now much interested in coronary intervention and, therefore, are not familiar with CVS-related angina. Since CVS may be complicated by lethal cardiac arrhythmias, sudden death, and incorrect management, it is very important for every physician to be alert to the presence of CVS, which is a dynamic type of coronary artery stenosis^[101,102]. With the correct diagnosis, we can manage CVS patients effectively and promptly, providing for optimal patient safety.

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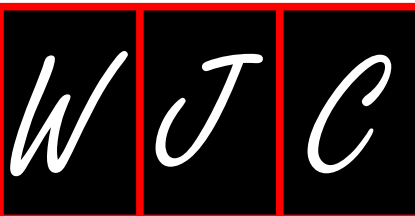
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Meetings

Events Calendar 2010

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Riyadh, Saudi Arabia
1st International Cardiovascular Pharmacotherapy Conference

January 17-21
Hollywood, United States
22nd Annual International Symposium on Endovascular Therapy

January 20-23
Sao Paulo, Brazil
World Cardiology, Metabolism and Thrombosis Congress

January 21-24
Phoenix, United States
13th Society for Cardiovascular Magnetic Resonance Annual Scientific Sessions

January 28-30
Brussels, Belgium
29th Belgian Society of Cardiology Annual Scientific Meeting

January 28-31
Nashville, United States
31st Annual Meeting of The American Academy of Cardiovascular Perfusion

February 3-6
Snowbird, United States
35th Annual Cardiovascular Conference at Snowbird

February 4-5
Leuven, Belgium
Leuven Symposium on Myocardial Velocity and Deformation Imaging

February 6-9
St. Petersburg, United States
10th Annual International Symposium on Congenital Heart Disease

February 8-10
Tel Aviv, Israel
10th International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy

February 11-12
London, United Kingdom
2nd National Chronic Heart Failure and Hypertension

February 18-21
Istanbul, Turkey
The 2nd World Congress on Controversies in Cardiovascular Disease (C-Care)

February 22-25
Maui, United States
Arrhythmias & the Heart Symposium

February 22-26
Cancun, Mexico
15th Annual Cardiology at Cancun-Advances in Clinical Cardiology and Multi-Modality Imaging

February 25-28
Valencia, Spain
First International Meeting on Cardiac Problems in Pregnancy

February 26-28
Hong Kong, China
International Congress of Cardiology

February 28-March 4
Scottsdale, United States
International Congress XXIII on Endovascular Interventions

February 28-March 5
Keystone, United States
Keystone Symposia: Cardiovascular Development and Repair (X2)

March 3-5
Kish Island, Iran
Islamic Republic of 4th Middle East Cardiovascular Congress

March 4-7
Newport Beach, United States
30th Annual CREF: Cardiothoracic Surgery Symposium

March 7-12
Snowmass Village, United States
Interventional Cardiology 2010: 25th Annual International Symposium

March 14-16
Atlanta, United States
American College of Cardiology 59th Annual Scientific Session

March 18-20
Rome, Italy
VIII Congress of the Italian Society of Cardiovascular Prevention

March 18-20
Prague, Czech Republic
XI International Forum for the Evaluation of Cardiovascular Care

March 24-25
Jeddah, Saudi Arabia
12th KFAFH Cardiovascular Conference: A balanced approach to treatment of cardiovascular diseases

April 8-11
Guangzhou, China
The 12th South China International Congress of Cardiology

April 14-15
Tel Aviv, Israel
The 57th Annual Congress of the Israel Heart Society in Association with The Israel Society of Cardiothoracic Surgery

April 15-18
Izmir, Turkey
59th European Society for Cardiovascular Surgery International Congress

May 5-7
Prague, Czech Republic
EuroPrevent 2010-Cardiovascular Prevention: a Lifelong Challenge

May 8-9
St. Paul, United States
Controversies in Cardiovascular Disease: Practical Approaches to Complex Problems: Medical and Surgical

May 12-16
Marrakesh, Morocco
7th Metabolic Syndrome, type II Diabetes and Atherosclerosis Congress

May 17-20
Whistler, Canada
6th IAS-Sponsored HDL Workshop on High Density Lipoproteins

May 21-22
Sydney, Australia
3rd Cardiovascular CT, Concord Conference 2010

May 29-June 1
Berlin, Germany
Heart Failure Congress 2010

June 1-4
Seoul, Korea, Republic of
9th Asian-Pacific Congress of Cardiovascular & Interventional Radiology (APCCVIR 2010)

June 16-19
Beijing, China
World Congress of Cardiology Scientific Sessions

June 17-19
Port El Kantaoui, Tunisia
The 7th Tunisian and Europeans Days of Cardiology Practice

July 1-3
Singapore, Singapore
6th Asian Interventional Cardiovascular Therapeutics Congress

July 16-19
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Frontiers in CardioVascular Biology 2010-1st Meeting of the CBCS of the ESC

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October 10-13
Rochester, United States
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October 16-19
Copenhagen, Denmark
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Boston, United States
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November 25-26
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December 9-11
Lisbon, Portugal
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Instructions to authors

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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/EID/eid.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, etc. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: <http://www.wjgnet.com/wjg/help/15.doc>.

Abbreviations

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, etc.

Restriction enzymes: *EcoRI*, *HindII*, *BamHI*, *Kho I*, *Kpn I*, etc.

Biology: *H. pylori*, *E. coli*, etc.

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