D.Novitzky, MD

EARLY ORGAN INJURY FOLLOWING EXPERIMENTAL BRAIN DEATH

Division of Cardiothoracic Surgery, University of South Florida
USA

The summary: Hemodynamic, endocrine and metabolic studies conducted on BD animals have confirmed a sequence of adverse events, which eventually will lead to a suboptimal function of the donor heart and other organs. Immediately following the induction of BD there is an adrenergic storm. This includes the release of endogenous cathecholamines and toxic tissue levels of epinephrine, which induces an acute myocardial ischemic injury. Hearts examined in this state under light microscopy show patchy diffuse injury of the subendocardium, conduction tissue, coronary arteries and various forms of myocytes necrosis as well as mononuclear cell infiltration.

Examination under electron microscopy confirms the presence of acute scattered cellular injury affecting mainly the sarcomere and the mitochondria. Following the cathecolamine storm, there is a reduction of plasma free triiodothyronine (FT3), free levothyroxine (FT4), cortisol, antidiuretic hormone (ADH), adrenocortical stimulating hormone (ACTH), normal thyroid stimulating hormone (TSH) and marked elevation of reverse triiodothyronine(T3). These events cause progressive inhibition of aerobic metabolic pathways, and lead to a reduction of myocardial tissue glycogen, adenosine triphosphate (ATP), creatine phosphate (CP) and lactate accumulation. The structural and metabolically injured heart then exhibits a reduction in contractility. Moreover, studies have demonstrated that hormonal replacement (T3, cortisol and insulin) in BD animals results in metabolic, biochemical and cardiac contractility recovery.

A similar plasma thyroid profile is also observed in animals subjected to cardiopulmonary bypass (CPB). This is associated with a significant high-energy phosphate depletion and lactate accumulation. It has been demonstrated that therapy with T3 reverses this myocardial dysfunction.

The administration of T3, cortisol and insulin to human brain injured organ donors allows rapid metabolic and hemodynamic recovery. Studies have confirmed that therapy with T3 alone has proven to be as efficient as hormonal therapy. Initially T3 is administered to the human BD organ donor and later to both the donor and recipient at the time of cardiac reperfusion. This results in acceptable functional recovery in the recipient even in initially marginal organ donors originally on high doses of inotropic support. By replacing T3, hearts, which were not initially considered viable for cardiac transplantation, were harvested with good outcomes in the recipient. The potential reversal of this injury by administering thyroid hormone creates a larger donor organ pool.

Induction of Brain Death

The first studies looking at the holistic effect of inducing brain death and its impact on donor organs were performed in Cape Town, South Africa. In a controlled experimental environment brain death was induced in the baboon by inflating a foley catheter placed in the subdural space (1) and in a pig by ligating the arteries arising from the aortic arch (2). Brain death was confirmed within minutes. Continuous hemodynamic and electrocardiographic recording and blood sampling were then performed for 24 hours (1). This confirmed a significant sympathetic response (3) within a few seconds following the induction of endocranial hypertension and subsequent brain death (Fig 1).

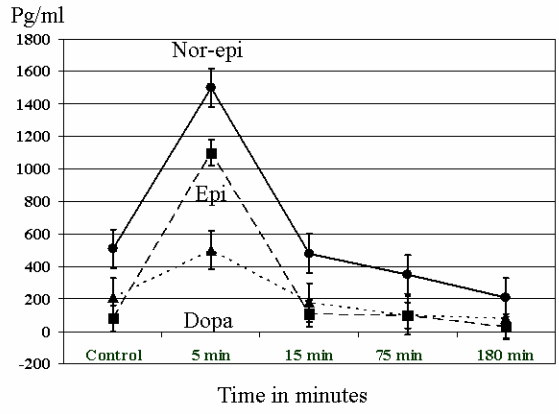

Fig. 1.
Increased plasma catecholamine levels observed following the induction of brain death.

The Autonomic Storm

Electrocardiographic Changes

Initially a parasympathetic (Stage I), vagal response is observed. This is characterized by sinus bradycardia, sinus node stand still, junctional escape ventricular beats and temporary heart block (Fig 2). The release of endogenous and circulating cathecholamines leads to stage II, characterized by sinus tachycardia without ST segment changes. As the sympathetic storm increases, Stage III occurs. Unifocal or multifocal ventricular ectopic beats and a run of ventricular tachycardia are then observed. During stage IV, sinus rhythm resumes and significant ischemic changes are observed. These include the occurrence of temporary Q waves and ST elevation similar to those observed in an acute myocardial infarction (Fig 3). Stage V marks the end of the autonomic storm. The heart is back in sinus rhythm, the ST segment changes are nonspecific, J waves are observed, the T wave may be flat or biphasic and right bundle branch block may occasionally be observed in animals.

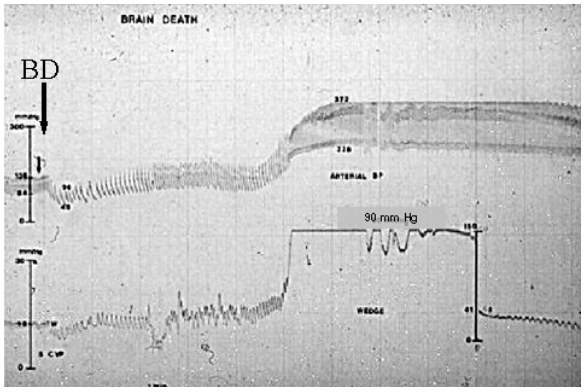

Fig. 2.
Electrocardiographic tracing during induction of brain death observed during Stage I.

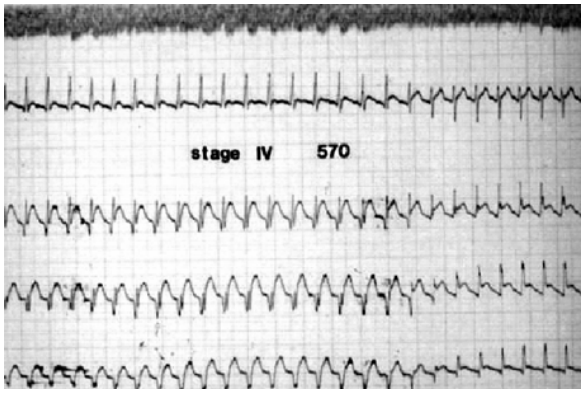

Fig. 3.
Ischemic electrocardiographic changes observed during stage IV.

The transient acute ischemic changes observed during Stages III and IV are the result of oxygen supply/ demand imbalance. In Stage V, the oxygen supply is restored and acute ischemia is resolved. During this initial phase the endogenous cathecholamines released initiate a cascade of adverse events. These events will have further negative impact on other organs, affecting the entire body including the activation of platelets, endothelium, and the release of pro-inflammatory cytokines (4, 5).

Hemodynamic Changes

In animals, the vagaly mediated initial impact of endocranial hypertension leads to a short-lived period of bradycardia and hypotension. After a few seconds, the release of endogenous and circulating catecholamines has a systemic effect on the entire body. Systemic blood pressure increases to high levels and usually lasts for the duration of Stages II, III and IV (Fig 4) and returns to control values or lower during stage V . In stages II and III, a sudden elevation in left atrial pressure is observed, which on occasion is up to 90 mm of Hg (6). This may well be related to cathecolamine induced papillary muscle ischemic dysfunction leading to temporary acute mitral valve regurgitation. Pulmonary injury may also occur at this time resulting in so-called "neurogenic pulmonary edema."(7) This is a reflection of papillary muscle dysfunction leading to short lived but devastating effects of mitral valve regurgitation. During this interval, the right atrial pressure remains unchanged. The cardiac output is significantly reduced during stages II, III, and IV and finally recovers by the end of stage V.

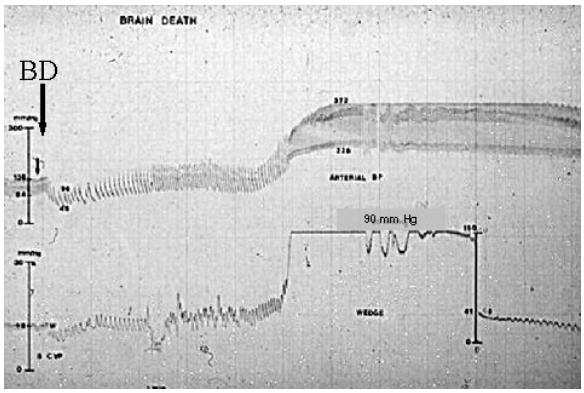

Fig. 4.
Hemodynamic response to endocranial hypertension. The upper tracing shows an increment of the systolic blood pressure of 372 mm of Hg. The lower tracing shows an increment of the left atrial pressure reaching 90 mm of Hg.

The observed hyperdynamic state following induction of brain death is directly attributed to the release of endogenous and circulating cathecholamines. This autonomic storm can be prevented with bilateral cardiac sympathectomy and by administer-

ing propranolol and verapamil prior to the induction of brain death (8). Autotransplantation of the heart renders it a dinnervated organ. Following the induction of brain death, in the baboon the heart is preserved. Although some degree of tachycardia is observed from increased circulating cathecholamines, the acute electrocardiographic ischemic changes noted in the whole animal are then abolished.

Histological Changes

Histological examination of organs procured from animals subjected to brain death confirm the occurrence of acute tissue injury. These are induced as a result of endogenous toxic cathecolamine levels. The injury is observed scattered throughout the entire heart affecting the myocardium of the atria, ventricles, conduction tissue, coronary artery system and the interstitum. The degree of injury is more severe at the left ventricular subendocardial level (9).

At this stage, various degrees and types of myocytes necrosis are noted. These are characterized by scattered foci, contraction band necrosis, myocytolysis and coagulative necrosis. Various degrees of mononuclear cell infiltrate around necrotic myocytes and capillaries are also seen. In the left ventricular sub endocardial area, the histological appearance resembles subendocardial necrosis similar to that found in an acute myocardial infarction.

The histology is similar to that observed in early biopsies procured from marginally functioning hearts. The loaded mononuclear cell infiltration surrounding the necrotic cells may be similar to the histological appearance of an acute rejection episode (10) (Fig 5).

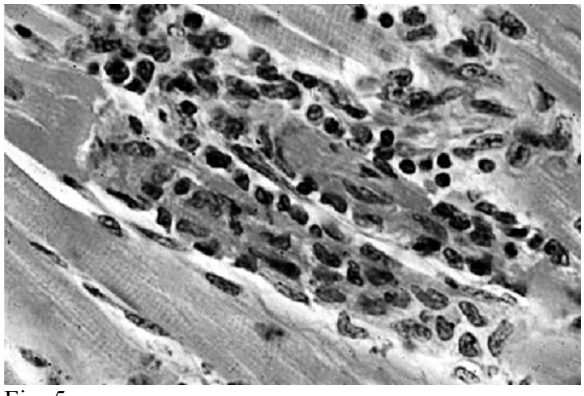

Fig. 5.
Mononuclear cell infiltrate surrounding necrotic myocytes.

The muscular media of the coronary artery system exhibits contraction band necrosis of the smooth muscle and deposits of calcium. This can be histologically observed using Van Kossa staining. The occurrence of crystallized calcium accumulation is a further indication of transient severe vasoconstriction that results from the toxic cathecolamine storm (9).

Pulmonary edema rich in protein and alveolar-septal hemorrhages are also found in the lungs (11). This occurs primarily in animals exhibiting high left atrial pressures (EKG stages II, III and IV). These changes are similar to those observed in patients with head injuries, pulmonary edema and normal wedge pressure. The catecholamine storm occurs in the patient in the field and at the site of the head injury. By the time of arrival at a hospital, the transient high left atrial pressure has normalized. However, the chest X-ray and oxygenation are found to be markedly abnormal.

Histological changes are also noted in the liver, kidneys and pancreas. Electron microscopy performed in specimens from animals and human donor hearts clearly show injury at the sarcomere and the mitochondria (12). There is a hypercontractile state and stretching-disruption of the sarcomeres (Fig 6). At the mitochondrial level, the organelle is filled with electron dense material, and the christii are disrupted or swollen. Redistribution of the mitochondria then takes place. Accumulation of mitochondria is seen mainly at the scalloped sarcolemma and in spaces left by the disrupted sarcomeres. Similar mitochondrial injury is also observed in the liver and kidneys.

Fig. 6.
Electron microscopy of a human donor heart displaying mitochondrial injury, multiple electron dense deposits, edema and membrane disruption.

Endocrine changes

Catecholamine activation of a 3-5 monodeiodinase rapidly affects the free thyroid hormone plasma levels. Free triiodothyronine (FT3), and levothyroxine (FT4) are observed to decline rapidly, and a significant elevation of rT3 is observed. During the monitoring period, TSH remains unchanged (1) (Fig 7). These changes in the thyroid profile are similar to those observed in the euthyroid sick syndrome (ESS) found in acutely ill patients (13).

In the baboon, rapid plasma decline is also noted in the cortisol, insulin, antidiuretic hormone and ACTH plasma levels.(1) This acute endocrine collapse is associated with generalized mitochondrial

injury. Cell injury at this point may have a major adverse impact on the organ's future functioning.

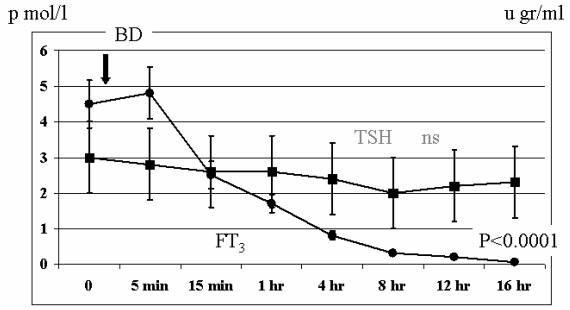

Fig. 7.
Plasma FT3 and TSH observed during and following induction of BD.

Hormonal Replacement in the Animal

A series of experiments have been conducted replacing the reduced hormones in BD animals. The hearts were then excised hearts and tested in a modified Langerndorf model using a support pig for blood oxygenation (2). The application of a modified working ex-vivo testing model has an advantage over the use of the whole animal. Since the hemodynamic data is collected under standardized loading conditions (preload and afterload), the results can be compared objectively. Hormonal replacement consists of the administration of T3 2mcg/h, cortisol 100 mg/h and insulin 10 IU/h for two hours (2).

A second series of comparable groups underwent an additional four hours of cold storage, and were then tested. Three groups of hearts were studied: hearts excised from a live animal, those that experienced brain death and those with brain death who received hormonal therapy (Fig 8).

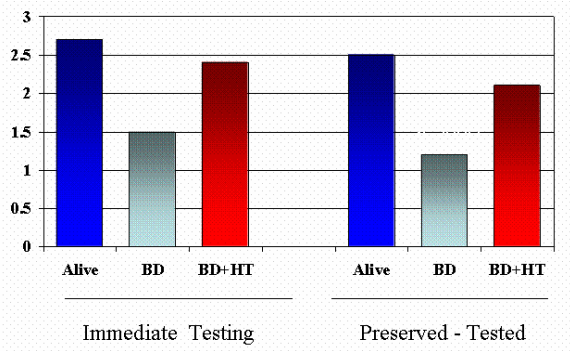

Fig. 8.
Ex vivo testing of the heart showing a significant reduction in cardiac output liters per minute in the hearts procured from alive animals, brain dead and brain dead receiving hormonal therapy.

Hearts procured from BD hormonally treated animals (non-stored and stored) clearly showed significant functional improvement when compared to those from untreated animals. Hemodynamic testing showed no difference in hearts procured from live animals. Following the testing of cardiac hemodynamics, myocardial biopsies were procured to conduct further biochemical analysis.

The myocardial tissue was then tested for glycogen, lactate, ATP and CP. Hearts from BD and hormonally treated animals exhibited no difference from biopsies obtained from live animals. However, the biochemical changes observed in BD untreated hearts showed significantly reduced levels of glycogen, ATP,CP and the elevation of tissue lactate.

Metabolic studies were performed in the whole animal 14C-R metabolites (U-glucose, pyruvate and palmitate) were administered intravenously to BD and BD-T3 treated animals (14). These studies confirmed a significant reduction of the plasma clearance, exhaled 14CO2 and prolonged half-life in the untreated BD animal. However, full metabolic recovery was observed in the BD-T3 treated baboon. The inability of the entire body to metabolize aerobically at the mitochondrial level is then demonstrated. The administration of T3 restored mitochondrial aerobic pathways, the exhaled CO2, from BD T3 treated animals was similar to that observed in live animals.

The functional ex-vivo testing, myocardial biopsies and the 14C-R metabolic studies clearly confirm the inhibition of aerobic pathways, which results from the deleterious impact of BD and full restoration following hormonal therapy.

Cardiopulmonary Bypass

The use of cardiopulmonary bypass (CPB) with its deleterious effect is essential in cardiac transplantation. The ESS induced by the CPB has been observed in a number of experimental animal studies (15). A low FT3 state may last for several days in humans (16). Myocardial biopsies performed prior to the initiation of CPB, at the completion of cardioplegic arrest, following the CPB run and three hours later confirmed high-energy phosphates reduction and myocardial lactate accumulation. No difference has been observed following T3 therapy at the time of removal of the aortic cross clamp to control pre-CPB values. Hearts of untreated animals were unable to sustain hemodynamic function after prolonged myocardial ischemia resulting in death. Animals treated with T3 at the time of cardiac reperfusion exhibited good hemodynamic function following the discontinuation of CPB (17).

Hormonal Replacement in the Patient

Two T3 treated BD organ donors were treated with an initial dose of 20 mcg as a bolus. Shortly thereafter, all inotropic support was discontinued in both donors. One developed tachycardia, hypertension, hyperthermia and retained CO2 and developed a thyrotoxic crisis. The second donor had similar but

milder adverse events. The heart from the first patient was not procured due to profound respiratory acidosis and the presence of ventricular arrhythmia. The heart from the second donor was procured with excellent function in the recipient. In view of the metabolic response observed in both patients the T3 dosage was reduced to an initial dose of 2 mcg/hr. This dose was then adopted, as the hemodynamic response was found to be adequate. The initial hormonal therapy consisted of a combination of T3 2 mcg/hr, cortisol 100 mg/hr and insulin 10 IU/hr for four hours or until the desired hemodynamic status was achieved. The initial evaluation of hormonal therapy in BD organ donors has been conducted on a small series of patients which have been compared with historical controls. The observed results consisted of a rapid hemodynamic and metabolic recovery (18).

The administration of T3 alone in human organ donors is efficacious in obtaining a similar response. It had been noted that patients needing the administration of high inotropic support require higher repetitive T3 dosing. Withdrawal of inotropic support improved hemodynamic function (20) to less than 10 mcg/kg/min.

Discussion

Induction of brain death in the experimental animal leads to a series of reproducible adverse events. Initially, there is a massive cathecolamine surge, which induces "Primary Injury" to cells and organs. This is followed by an endocrine-metabolic derangement ("Secondary Injury"), and progressive inhibition of aerobic pathways. In addition, this leads to cellular depletion of high energy phosphates, which is an essential substrate for multiple ATPases at various cellular levels and leads to further calcium induced injury.

The low FT3 state characteristic of the ESS is always present. Clinically the lower the FT3/rT3 ratio correlates with poor patient outcome (19). This has been documented with the occurrence of sepsis (20), acute myocardial infarction (21), hemorrhagic shock (22, 23) and in patients with multi-organ failure (24).

Primary and secondary injuries initiate a cascade of adverse events that include the release of pro-inflammatory cytokines, activation of endothelium and platelets, production of oxygen free radicals, expression of tissue antigens and other events (4,5). This sets the stage for further tissue injury in the donor and in the recipient at the time of organ reperfusion (25). In the recipient, further tissue injury may result in primary graft failure.

Although the use of T3 replacement has been initially strongly criticized, research and clinical data strongly supports its use not only in unstable but also in stable donors. Furthermore, T3 has been found to have a beneficial impact on the heart of baboons (15) and pigs (17) subjected to cardioplegic arrest on CPB, reversal of the stunned myocardium in dogs (26,27) and in patients who became CPB dependant following open-heart surgery (28). T3 has also been shown to be beneficial in reducing the dose of insulin in diabetic coma and in decreasing the anuric period in patients with acute renal failure (29).

At the cellular level, T3 has an impact on multiple sites. The immediate effects are non-genomic (30) and the late DNA-RNA-protein are synthesis related (31). The non-genomic affects of upregulation of beta-receptors (32), activation of sacolemmal, SR calcium channels (33), Na-K channels (34, 35), directly effect the stimulation of aerobic metabolism, thus allowing restoration of cellular high energy phosphates, inhibition of pro-inflammatory cytokines and normalization of cytosolic calcium levels (33).

Some transplant centers have implemented the use of thyroid hormones in the management of BD organ donors (36, 37, 38). However, further prospective randomized clinical studies are required to confirm the beneficial effects of T3 therapy on both the donor and the recipient (39). This may eventually become an essential component in the management of organ donors, thereby allowing hemodynamic stabilization and the reduction of inotropic support and therapy. The application of this management strategy will provide an increased reservoir of donors and enlarge the pool of available organs for transplantation.

REFERENCES

1. Novitzky D, Wicomb WN, Cooper DKC, Rose AG, Fraser RC, Barnard CN. Electrocardiographic, hemodynamic and endocrine changes occurring during experimental brain death in the Chacma baboon. J Heart Transplant 1984;4:63-9.
2. Novitzky D, Wicomb WN, Cooper DKC, Tjaalgard MA. Improved cardiac function following hormonal therapy in brain-dead pigs: relevance to organ donation. Cryobiology 1987;24:1-10.
3. Cushing H. Some experimental and clinical observations concerning states of increased endocranial tension. Am J Med Sci 1902;124:373.
4. Pratschke J, Wilhelm MJ, Kusaka M, Hancock WW, Tilney NL. Activation of proinflammatory genes in somatic organs as a consequence of brain death. Transplant Proc 1999;31:1003-5.
5. Stangl M, Zerkaulen T, Theodorakis J, Illner W, Schneeberger H, Land W, Faist E. Influence of brain death on cytokine release in organ donors and renal transplants. Transplant Proc 2001;33(1-2):1284-5.
6. Novitzky D, Cooper DKC, Wicomb WN, Reichart B. Brain death-induced hemodynamic changes resulting in cardiac pulmonary injury in the baboon. Transplant Proc 1986;18:1190-2.
7. Novitzky D, Cooper DKC, Wicomb WN, Reichart B. Hemodynamic changes, myocardial injury and pulmonary edema induced by sympathetic activity during the development of brain death in the baboon. Transplant Proc 1986;18:609-12.
8. Novitzky D, Cooper DKC, Rose AG, Reichart B. Prevention of myocardial injury by pretreatment with verapamil hydrochloride prior to experimental brain death: efficacy in a baboon model. Amer J Emerg Med 1987;15:11-18.
9. Rose AG, Novitzky D, Factor SM. Catecholamine-associated smooth muscle contraction bands in the media of coronary arteries of brain-dead baboons. Am J of Cardiovasc Pathol 1988;2:63-7.
10. Novitzky D, Rose AG, Cooper DKC, Reichart B. Histopathological changes at the site of endomyocardial biopsy: potential for confusion with acute rejection. J Heart Transplant 1986;5:79-80.
11. Novitzky D, Wicomb WN, Rose AG, Cooper DKC, Reichart B. Pathophysiology of pulmonary edema following experimental brain death in the Chacma baboon. Ann Thorac Surg 1987;43:288-94.
12. Novitzky D, Rhodin J, Cooper D, Ye Y, Min K-W, De-

bault L. Ultrastructural changes associated with brain death in the human donor heart. Transplant International June 1995.
13. McIver B, Gorman CA. Euthyroid sick syndrome: an overview. Thyroid 1997;1:125-32.
14 Novitzky D, Cooper DKC, Morrell D, Isaacs S. Change from aerobic to anaerobic metabolism after barin death, and reversal following triiodothyronine therapy. Transplantation 1988, 45: 32-36.
15 Novitzky D, Human PA, Cooper DKC. Effect of triiodythyronine (T3) on myocardial high-energy phosphates and lactates following ischemia and cardiopulmonary bypass-an experimental study in baboons. J Thorac Cardiovasc Surg 1988;96:600-607.
16 Holland FW 2nd, Brown PS JR, Weintraub BD, Clark RE. Cardiopulmonary bypass and thyroid function: a "euthyroid sick syndrome". Ann Thorac Surg 1991;52(1):46-50.
17 Novitzky D, Human P, Cooper D. Inotropic effect of triiodothyronine following myocardial ischemia and cardiopulmonary bypass: an experimental study in pigs. Ann Thorac Surg 1988, 45:45-50.
18 Novitzky D, Cooper DKC, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. Transplantation 1987;43:852-4.
19 Schilling JU, Zimmermann T, Albrecht S, Zwipp H, Saeger HD. Low T3 syndrome in multiple trauma patients-a phenomenon or important pathogenetic factor? Med Klin 1999;94 Suppl 3:66-9.
20 Alazzo MG, Suter PM. Delivery dependent oxygen consumption in patients with septic shock: daily variations, relationship with outcome and the sick-euthyroid syndrome. Intensive Care Med 1991;17(6):325-32.
21 Dyke CM, Yeh T JR, Lehman JD, Abd-Elfattah A, Ding M, Wechsler AS, Salter DR. Triiodothyronine-enhanced left ventricular function after ischemic injury. Ann Thorac Surg 1991;52(1):14-9.
22 Shigematsu H, Smith RA, Shatney CH. Triiodothyronine increases survival in canine hemorrhagic shock. Resuscitation 1987;15(4):233-43.
23 Vitek V, Shatney CH, Lang DJ, Cowley RA. Thyroid hormone responses in hemorrhagic shock: study in dogs and preliminary findings in humans. Surgery 1983;93(6):768-77.
24 Slag MF, Morley JE, Elson MK, Crowson TW, Nutthall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 1981:245:43-5.
25 Menger MD. Microcirculatory disturbances secondary to ischemia-reperfusion. Transplant Proc 1995;25:2863.
26 Novitzky D, Matthews N, Shawley D, Cooper DKC, Zhudi N. Tiiodothyrononine in the recovery of stunned myocardium in dogs. Ann Thorac Surg 1991,51:10-7.
27 Salter DR, Dyke CM, Wechsler AS. Triiodothyronine (T3) and cardiovascular therapeutics: a review. J Cardiac Surg 1992;7:363-74.
28 Novitzky E, Cooper DK, Swanepoel A. Inotropic effect of triiodothyronine (T3) in low cardiac output following cardioplegic arrest and cardiopulmonary bypass: an initial experience in patients undergoing open heart surgery. Eur J Cardiothorac Surg 1989;3(2):140-5.
29 Piennar H, Schwartz I, Roncone A, Hickman R. Function if kidney grafts from brain dead donor pigs. Transplantation 1990;50:580.
30 chmidt BM, Martin N, Georgens AC, Tillmann HC, Feuring M, Chridt M, Wehling M. Nongenomic cardiovascular effects of triiodothyronine in euthyroid male volunteers. J Clin Endocrinol Metab 2002;87(4):1681-6.
31 Anderson GW, Mariash CN, Oppenheimer JM. Molecular actions of thyroid hormones. The Thyroid. Lippincott, Williams and Wilkens, A Walter Kluver Company, Philadelphia 2000;174-95.
32 Yin Y, Vassy R, Nicolas P, Perret GY, Laurent S. Antagonism between T3 and amiodarone on the contractility and the density of beta-adrenoceptors of chicken cardiac myocytes. Eur J Pharmacol 1994;261(1-2):97-104.
33 Warnick PR, Davis PJ, Davis FB, Cody V, Galindo J Jr, Blas SD. Rabbit skeletal muscle sarcoplasmic reticulum Ca(2+)-ATPase activity: stimulation in vitro by thyroid hormone analogues and bipyridines. Biochim Biophys Acta 1993;1153(2):184-90.
34 Huang CJ, Geller HM, Green WL, Craelius W. Acute effects of thyroid hormone analogs on sodium currents in neonatal rat myocytes. J Mol Cell Cardiol 1999;31(4):881-93.
35 Dudley SC, Baumgarten CM. Physiologic concentracions of triiodo-L-thyronine increase bursting of Na+ channels. Biophys J 1991;59:98.
36 Taniguchi S, KitamuraS, Kawaci K, Doi Y, Aoyama N. Effects of hormonal supplements on the maintanance of cardiac function in potential donor patients after cerebral death. Eur J Cardio-Thorac Surg 1992:6:96-102.
37 Jeevanandam V, Todd B, Hellman S, Eldridge C, Mcclurken J, Addonizio VP. Use of triiodothyronine replacement therapy to reverse donor Myocardial dysfunction: creating a larger donor pool. Transplant Proc 1993;25(6):3305-6.
38 Zaroff JG, Rosengard BR, Armstrong WF, Babcock WD, D'Alessandro A, Dec GW, Edwards NM, Higgins RS, Jeevanandum V, Kauffman M, Kirklin JK, Large SR, Marelli D, Peterson TS, Ring WS, Robbins RC, Russell SD, Taylor DO, Van Bakel A, Wallwork J, Young JB. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, Va. Circulation 2002;106(7):836-41.
39 Novitzky D, Cooper DKC, Chaffin JS, Greer AE, Debault LE, Zuhdi N. Improved cardiac allografts function following triiodothyronine (T3) therapy to both donor and recipient. Presented to the American Society of Transplant Surgeons, Chicago 1989. Transplantation 1990;49:311-6.

Д.Новицкий

РАННИЕ ПОВРЕЖДЕНИЯ ОРГАНОВ ПОСЛЕ МОЗГОВОЙ СМЕРТИ В ЭКСПЕРИМЕНТЕ

Университет Южной Флориды
США

Гемодинамические, эндокринные и метаболические исследования, проведенные на животных после мозговой смерти (МС), подтвердили последовательность неблагоприятных событий, которые в конечном счете приводят к нарушению функции донорского сердца и других органов. Сразу после МС происходит адренергический шторм. Это включает выброс эндогенных катехоламинов и достижение токсичных уровней тканевого эпинефрина, что стимулирует острую миокардиальную ишемическую недостаточность. Исследование сердец после МС под световой микроскопией выявили очаговые диффузные изменения субэндокарда, проводящей системы, коронарных артерий, различные формы некроза миоцитов и мононуклеарную инфильтрацию.

Исследование под электронной микроскопией подтверждает острое повреждение клеток, главным образом саркомер и митохондрий. После выброса катехоламинов происходит уменьшение плазмы, высвобождение гормонов щитовидной железы, антидиуретического и адренокортикотропного гормонов. Всё это вызывает постепенное торможение аэробных метаболических процессов и метаболические нарушения в миокарде, приводящие к снижению его сократимости.

Подобные изменения наблюдались у животных при экстрапульмональном кровообращении. Доказано, что терапия с применение Т3 полностью восстанавливает описанную миокардиальную дисфункцию.

Исследования на людях подтвердили, что терапия с применением Т3 может быть столь же эффективной, как и гормональная терапия. Последовательная терапия Т3, проводимая у реципиента и донора, позволяет сохранить приемлемую эвакуаторную функцию миокарда при пересадке сердца.

Dimitri Novitzky, MD - Professor of Surgery, Division of Cardiothoracic Surgery, University of South Florida
Correspondence: Dimitri Novitzky, MD, 4 Columbia Drive, Suite 650, Tampa FL 33606, USA
E-Mail: Novitzky@aol.com