Mitochondrial Disease(s) & Dysfunction
by
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In the previous report we discussed how cellular energy is produced in the human cell. More specifically it is the mitochondria within the human cell that is responsible for producing the bulk (90%) of the body’s “energy currency” – ATP (adenosine triphosphate). Also mentioned is the fact that there is a direct relationship between the efficiency of ATP production within the cell and overall personal health.

When mitochondria are producing optimal levels of ATP... life is good. But when mitochondria fail or become dysfunctional... less and less energy is generated within the cell. Cell injury and even cell death follow. If this process is repeated throughout the body, whole systems begin to fail, and the life of the person in whom this is happening is severely compromised... both physically and mentally.

“Primary” Mitochondrial Disease(s) & Dysfunction

The terms mitochondrial “disease” and mitochondrial “dysfunction” are sometimes used interchangeably to describe poorly functioning mitochondria. The major difference takes place in determining whether or not it is a “primary” or “secondary” mitochondrial disease.

Primary mitochondria diseases are the result of either inherited or spontaneous mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) which lead to altered functions of the proteins or RNA (ribonucleic acid) molecules that normally reside in mitochondria. Meaning... it’s genetic. This results in a chronic disorder characterized by the inability of the mitochondria to produce enough energy for proper cell or organ function.

Secondary mitochondrial disease is always related to another disorder or illness which causes mitochondria to malfunction despite the normal formation of mitochondria.

“It takes about 3000 genes to make a mitochondrion. Mitochondrial DNA encodes just 37 of these genes; the remaining genes are encoded in the cell nucleus DNA and the resultant proteins are transported to the mitochondria. Only about 3% of the genes necessary to make a mitochondrion (100 of the 3000) are allocated for making ATP. More than 95% (2900 of 3000) are involved with other functions tied to specialized duties.
These specialized duties or non-ATP-related functions are intimately involved with most of the major metabolic pathways used by a cell to build, break down, and recycle its molecular building blocks. Cells cannot even make the DNA and RNA they need to grow and function without mitochondria.

“Because mitochondria perform so many different functions in different tissues, there are literally hundreds of different types of mitochondrial diseases.”

Mitochondrial diseases are even more complex in adults because detectable changes in mtDNA occur as we age and, conversely, the aging process itself may result from deteriorating mitochondrial function. There is a broad spectrum of metabolic, inherited and acquired disorders in adults in which abnormal mitochondrial function has been demonstrated.

**Informative Publications, Websites & Videos**

As mentioned there are hundreds of primary mitochondrial diseases and it is beyond the scope of this report to list them all. Instead I have provided links to informative publications and websites that specialize in mitochondrial diseases which list some of these disorders.

Also found on these sites are lists of the possible symptoms associated with mitochondrial diseases. Along with this information you’ll find information about testing and treatment for mitochondrial diseases. Some key points found at these links for primary mitochondrial diseases are:

- The list of symptoms which accompany a patient with mitochondrial disease is **long** - due in part to the fact that mitochondria exist in every cell in the body (except blood). Meaning, mitochondrial disease can affect any organ(s) or organ systems - making it a systemic disorder.

  The long list of symptoms revolves around one primary factor; that being the lack of cellular energy production – cellular fatigue - which predominately affects the neural, muscular & cardiac tissues.

- There is no definitive test and what testing exists is not considered to be accurate. Though there is hope for more thorough genetic testing in the future.

- Mitochondrial diseases are difficult to diagnose – due to the long list of symptoms which patients present a doctor with and the lack of accurate testing. Plus the fact that there are very few doctors who specialize in these diseases with the remaining doctors unaware of such a diseases.

- At this time, there are no cures. Treatment is usually with supplements.

  “Many experts refer to Mitochondrial Disease as the "Notorious Masquerader" because it wears the mask of many different illnesses.”
[Link](#)

"Mitochondrial disease (MD) can be a complex, debilitating, life-threatening condition in its severest forms. It affects both children and adults. Mitochondrial disease in adults is more often associated with mutations in mtDNA, whereas the majority of nDNA mutations causing MD present in childhood. Because mitochondria are present in almost every tissue (except for red blood cells), MD can potentially affect any organ in the body. Due to this clinical variability, MD is potentially difficult to diagnose, often being under recognized or misdiagnosed...

... The respiratory chain is unique as it is under dual genomic control, with subunits for Complexes I, III, IV, and V encoded for by both nDNA and mtDNA. Complex II, however, is exclusively encoded by nDNA. Therefore, mutations in genes related to the respiratory chain from both the mitochondrial and nuclear genomes can disturb mitochondrial function...

... Pathogenic mutations in mtDNA can potentially alter mitochondrial function in any organ or tissue of the body. A database of reported mtDNA mutations can be found at [www.mitomap.org](http://www.mitomap.org). Despite the large number of pathogenic mtDNA mutations in humans, only a few occur frequently in various human populations: m.3243A> G (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), m.1555A> G (aminoglycoside-induced hearing loss), m.8344A> G (myoclonus epilepsy and ragged-red fibers [MERRF]), m.8993T> G (neuropathy, ataxia, and retinosis pigmentosa [NARP]), m.3460A> G, m.11778A> G, and m.14484C> T (Leber's hereditary optic neuropathy [LHON])."

Mitochondrial Cytopathy in Adults: What We Know So Far by Bruce Cohen & Deborah Gold, *Cleveland Clinic Journal of Medicine*, July;68(7):625-642 (2001)  
[Link](#)

"Symptoms in adults tend to develop over years and therefore it is distinctly uncommon for these diseases to be diagnosed when symptoms first begin. The early phase can be mild and may not resemble any known mitochondrial disease. In addition, symptoms such as fatigue, muscle pain, shortness of breath and abdominal pain can easily be mistaken for collagen vascular disease, chronic fatigue syndrome, fibromyalgia, or psychosomatic illness."

“We identified 174 nuclear-encoded mitochondrial genes associated with 191 diseases”


“The causes of neuronal dysfunction and cell death are varied and may follow a number of distinct pathways in each of these disease processes. As discussed above, it is self-evident that mitochondrial dysfunction will manifest itself as cellular dysfunction or death. Impaired ATP generation will cause a failure of cellular homeostasis, with attendant changes in the ionic balance for Na⁺, K⁺, Cl⁻ and Ca²⁺ that will disturb the patterning of electrical signals and of the intracellular [Ca²⁺] signals that together underpin the transmission of information in the CNS. Ultimately, ATP depletion will lead to necrotic cell death”.


“Over the last decade we have come to realize that mitochondrial DNA (mtDNA) defects are far more common than was previously anticipated. Many mtDNA defects present to general physicians and pediatricians with symptoms and signs which at first glance are indistinguishable from other more common diseases. The presence of unusual patterns of multi-organ involvement, although subtle, should lead to a high index of suspicion of mitochondrial disease…


“Many mitochondrial disorders are so new that they have not yet made it into the medical textbooks or in some cases, the medical literature. Consequently, most physicians are not able to recognize them reliably. Even physicians working in highly specialized referral centers who see dozens of cases of mitochondrial disease every year are struck by the great diversity of signs and symptoms of these diseases...

... The primary care physician should remember this relatively simple rule of thumb – When a common disease has features that set it apart from the pack or involves 3 or more organ systems, think mitochondria”
**Websites:**

- North American Mitochondrial Disease Consortium, *by NIH*, [List of Mitochondrial Diseases](Link)
- Mitochondria Research Society, [List of Mitochondrial Diseases](Link)
- United Mitochondrial Disease Foundation (UMDF) [Lots of Information](Link)
- Foundation for Mitochondrial Medicine [Link]
- MitoAction [Link]

**Videos – Medical Information & Personal Stories:**

- UMDF Interview with Gene Dx (webcast) *Very Informative* [Link] (11:30)
- UMDF Interview with Dr. Kendall (webcast) *Very Informative* [Link] (31:00)
- The Faces of Mitochondrial Disease - Pam, The UMDF Channel [Link] (2:02)
- The Faces of Mitochondrial Disease - Kathy, The UMDF Channel [Link] (2:36)
- The Faces of Mitochondrial Disease – The Swinns, The UMDF Channel [Link] (2:59)
- Mitochondrial Disease, fourgirls1boy4me’s channel [Link] (11:49)
- Living with Mitochondrial Disease, MitoAction Channel [Link] (10:01)
- This is My Mito, MitoAction Channel [Link] (1:02)
“Secondary” Mitochondrial Disease(s) & Dysfunction

As mentioned, mitochondrial disease can be classified as primary or secondary. Up until recently, when the medical profession talked of mitochondrial disease, they usually were talking about the primary type. That is, the type caused by a genetic mutation in the genes used to make the mitochondria.

However, the secondary type of mitochondrial disease, which is related to another illness, is now being discovered to be a major factor in more and more neuro-endo-immune disorders/illnesses such as:

- Chronic Fatigue Syndrome
- Multiple Chemical Sensitivity
- Cardiomyopathy
- Alzheimer’s Disease
- Huntington’s Disease
- Parkinson’s Disease
- Diabetes
- Hypothyroidism
- Autism
- Asthma
- Irritable Bowel Syndrome
- ETC.

Unfortunately, mitochondrial diseases are difficult to diagnose. Thus causing a lot of confusion as to whether a mitochondria disease in a particular patient is primary or secondary. Or whether or not the long list of symptoms presented by a patient… is indeed a mitochondrial disease or another type of medical disorder with similar symptoms.

One determining factor in mitochondrial dysfunction is the hallmark symptom of: Post-Exertional Malaise. This simply means a person will “crash” after “pushing” themselves, either physically, mentally or emotionally. Post-exertional malaise or crashing can last several days to several months depending on the severity of a person’s medical condition and how much a person pushed themselves. During these periods a person is usually house bound or even bedridden while they attempt to recuperate to a semi-functional level.

One of the organs in the body which is impacted most by the effects of post-exertional malaise is the heart. This makes sense, because cardiac tissue contains the highest concentration of mitochondria. Because cardiac tissue is (debatably) the most metabolically active tissue in the body, cardiac myocytes (heart cells) contain mitochondria in the order of several thousand per myocyte.

This is in comparison to neural cells which contain only a handful of mitochondria per neuron. This low number of mitochondria, however, is what also makes neurons more vulnerable... no reserves. This is also why many of the symptoms and disorders associated with mitochondrial dysfunction are neurological in nature.
There is a tremendous amount of information available showing the association between many of the neuro-endo-immune disorders and mitochondrial dysfunction. Despite this, I have decided to focus mainly on the subject of post-exertional malaise and heart failure (with most of the work coming from the area of Chronic Fatigue Syndrome) for reasons given above.

Therefore, the list of scientific publications (below) is related to mitochondrial dysfunction which for right now would be considered secondary in nature. It should be noted; between the information provided for primary mitochondrial disease and the partial list of secondary mitochondrial disease publications below - this should be ample enough information to indicate that mitochondrial disease(s) and dysfunction is a key piece to solving the puzzle of neuro-endo–immune disorders.

**Post-Exertional Malaise & Mitochondrial Dysfunction**

*David Bell MD*

- **ME/CFS as a Mitochondrial Disease**, by David Bell, *Lyndonville News*, Link

  “While I agree that ME/CFS is a mitochondrial disease, this term needs clarification because ME/CFS is a mitochondrial disease like no other...

  ... Until recently, when a child was diagnosed as having a mitochondrial disease, it was a disaster, even a death sentence, for it meant that there were major abnormalities in the mitochondrial or nuclear DNA that regulated energy production. Without energy (ATP) it is impossible to survive...

  ... This is what most clinicians think of when the words mitochondrial disease is mentioned, but these illnesses do not, in general, apply to ME/CFS...

  ... There is another form of mitochondrial disease, or secondary mitochondrial disease. In secondary mitochondrial disease the primary problem is not with the mitochondria, but some other problem messes up mitochondrial function. There are many illnesses where the primary defect ends up causing problems with the generation of energy in mitochondria...

  ... As clinicians have observed, the symptom of “post-exertional malaise” is one of the most distinguishing features of CFS.”
“We observed that CFS patients as a group have reduced cardio-respiratory reserve with a lower anaerobic threshold than sedentary controls. This finding replicates previous studies. One implication of a lowered anaerobic threshold would be increased reliance on anaerobic as opposed to aerobic metabolism with a predicted consequence of increased short-term acid generation within muscle as a result of over utilization of the lactate dehydrogenase pathway. This prediction was confirmed by the use of MR spectroscopy methodologies which demonstrated increased post exercise acidosis in the CFS group as a whole.”

“This phenomenon, which is also a feature of mitochondrial disease where increased proton efflux after exercise helps compensate for reduced aerobic capacity, was absent from the CFS patients. These findings suggest that CFS patients are unable to compensate for the increased reliance upon anaerobic energy sources during muscle contraction in comparison with other conditions with reduced aerobic capacity...

...Using this approach, total post exercise acid exposure is of the order of 50-fold higher in CFS patients exercising to the same degree as normal controls, with no reduction in this pattern of sustained high level acidosis with repeat exercise. We believe that the local and systemic sequelae of this sustained acid exposure contribute significantly to the expression of fatigue in CFS.

“Chronic fatigue syndrome patients undertaking MVC (maximal voluntary contraction) fell into two distinct groups: 8 (45%) showed normal PCr (phosphocreatine) depletion in response to exercise at 35% of MVC; 10 CFS patients had low PCr depletion. The CFS whole group exhibited significantly reduced anaerobic threshold, heart rate, VO₂, VO₂ peak and peak work compared to controls...

... Resting muscle pH was similar in controls and both CFS patient groups. However, the CFS group achieving normal PCr depletion values showed increased intramuscular acidosis compared to controls after similar work after each of the three exercise periods with no apparent reduction in acidosis with repeat exercise of the type reported in normal subjects. This CFS group also exhibited significant prolongation (almost 4-fold) of the time taken for pH to recover to baseline.”

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“At both exercise tests the patients reached the anaerobic threshold and the maximal exercise at a much lower oxygen consumption than the controls and this worsened in the second test. This implies an increase of lactate, the product of anaerobic glycolysis, and a decrease of the mitochondrial ATP production in the patients...

... the oxidative phosphorylation... was similar in CFS/ME patients and controls. The plasma creatine kinase levels before and 24 h after exercise were low in patients and controls, suggesting normality of the muscular mitochondrial oxidative phosphorylation.”

“There were significant differences between the patients and controls. Based on the oxygen uptake test, the patients not only performed worse than controls in the first test, but the recovery after 24 h was not completed in this group as well. This indicates an impaired recovery, as expressed in the criterion “post-exertional malaise” of the CDC Symptom score.”

“A limited mitochondrial ATP synthesis was the working hypothesis for this investigation. This is probably not true, as the energy production can be limited by other mechanisms as well. The exercise tests with increased work load suggested the possibility that the mitochondrial ATP synthesis was decreased, because the anaerobic threshold was reached. Then the mitochondria were no longer able to produce sufficient ATP to sustain the exercise, and the anaerobic glycolysis in muscle had to produce the extra ATP needed, which is reflected by the lactate production.”

“Conclusion - The decrease in mitochondrial ATP synthesis in the CFS/ME patients is not caused by a defect in the enzyme complexes catalyzing oxidative phosphorylation, but in another factor.”

“The decrease in mitochondrial ATP production at increasing work rate, detected by the CPET tests in the present well-characterized though small group of CFS/ME patients, is a secondary phenomenon.”
Recovery time from the exercise test was markedly different between the two groups. **Within 24 hours of the test, none of the CFS patients indicated full recovery in contrast to 20 controls (87%).** After 2 days, all control subjects reported full recovery from the test, whereas only 1 CFS patient (4%) felt recovered by that time. Notably, although the entire control group recovered within 2 days, **15 CFS patients (60%) reported that it took ≥5 days to fully recover from the test. Some of them felt that even after the full week, they had not yet recovered...**

... In contrast to the experience of the CFS group, of the 20 controls who indicated full recovery within 24 hours, 17 actually reported feeling an increased sense of well-being relative to before the test, which they directly attributed to post testing exercise effect...

... Another interesting difference between groups was the reported symptom of cognitive dysfunction, for example, “brain-fog” or “difficulty concentrating.” Problems of this nature were not reported by any of the control subjects, whereas 12 patients (48%) experienced these problems...

... there are substantial data implicating **metabolic anomalies or autonomic dysfunction** as the source of decreased functional capacity in CFS patients.”

**Conclusion:** In the absence of a second exercise test, the lack of any significant differences for the first test would appear to suggest no functional impairment in CFS patients. However, the results from the second test **indicate the presence of a CFS related post-exertional malaise...**

... Deconditioning in CFS patients has been suggested to explain the relatively low performance of CFS patients. The profound reduction in physical activity that accompanies CFS symptoms certainly results in deconditioning. In isolation, the similarity of results between patients and controls for the first test in this study do not contradict a deconditioning hypothesis for CFS performance. However, the fall in oxygen consumption among the CFS patients on the **second test appears to suggest metabolic dysfunction rather than a sedentary lifestyle** as the cause of diminished exercise capacity in CFS...
Low exercise performance among CFS patients is sometimes discounted with allegations of poor effort or malingering on the test precipitated by an irrational fear of physical activity, or kinesiophobia. However, all patients in the present study met criteria for maximal effort on both exercise tests...

Where maximal effort is given on both tests, a finding of reduced oxygen consumption on the second test clearly illustrates oxidative and/or metabolic dysfunction.”

### Heart Failure & Mitochondrial Dysfunction

**Sarah Myhill MBBS**

- **CFS – The Central Cause: Mitochondrial Failure** by Sarah Myhill
  - [Sarah Myhill’s Website](#) (updated 2011) [Link](#)

  “ATP recycles approximately every 10 seconds in a normal person - if this goes slow, then the cell goes slow and so the person goes slow and clinically has poor stamina i.e. CFS.”

  “Problems arise when the system is stressed. If the CFS sufferer asks for energy faster than he can supply it, (and actually most CFS sufferers are doing this most of the time!) ATP is converted to ADP faster than it can be recycled. This means there is a build-up of ADP. Some ADP is inevitably shunted into *adenosine monophosphate (AMP)*. But this creates a real problem, indeed a metabolic disaster, because AMP, largely speaking, cannot be recycled and is lost in urine.”

  “If mitochondria do not work properly, then the energy supply to every cell in the body will be impaired. This includes the heart. Many of the symptoms of CFS could be explained by heart failure because the heart muscle cannot work properly. Cardiologists and other doctors are used to dealing with heart failure due to poor blood supply to the heart itself. In CFS the heart failure is caused by poor muscle function and therefore strictly speaking is a *cardiomyopathy*. This means the function of the heart will be very abnormal, but traditional tests of heart failure will be normal.

  “Thanks to work by Dr Arnold Peckerman [SEE BELOW] we now know that cardiac output in CFS patients is impaired. Furthermore the level of impairment correlates very closely to the level of disability in patients.
“The two key symptoms in patients with CFS which I believe reflect mitochondrial dysfunction are:

1. Very poor stamina (mental and physical) – i.e. you can do things, but only for about 5 seconds before tiring. This is due to slow recycling of ATP.

2. Delayed fatigue (mental and physical) – i.e. symptoms persist for 24 - 96 hours if you over-do things. This is because when mitochondria are stressed, all the energy molecules (ATP, ADP and AMP) are drained out.

“If ATP levels drop as a result of leakage of AMP, the body has to make brand new ATP. ATP can be made very quickly from a sugar called D-ribose, but D-ribose is only slowly made from glucose (via the pentose phosphate shunt). This takes anything from one to four days. So this delay is one possible explanation for the biological basis of delayed fatigue.

However, there is another problem. If the body is very short of ATP, it can make a very small amount of ATP directly from glucose by converting it into lactic acid. This is exactly what many CFS sufferers do and, indeed, we know that CFS sufferers readily switch into anaerobic metabolism.

However, this results in two serious problems – lactic acid quickly builds up especially in muscles to cause pain, heaviness, aching and soreness (“lactic acid burn”), secondly no glucose is available in order to make D-ribose! So new ATP cannot be easily made when you are really run down. Recovery takes days!

Worse than that, lactic acid has to be converted back to pyruvate in order to repeat the citric acid cycle – but this requires a lot of energy (ATP) and the ATP is not there. So lactic acid hangs about for a long time causing pain.”

“When John McLaren-Howard does the translocator (TL) protein function tests he often finds lactic acid stuck onto mitochondrial membranes – this illustrates one of the many vicious cycles in CFS – if TL protein is blocked by lactic acid, mitochondria work less efficiently and therefore one is more likely to switch into anaerobic metabolism and produce more lactic acid!”
“Furthermore, brain cells are not particularly well stocked with mitochondria and therefore they run out of energy very quickly. Brain mitochondria are particularly dependent on blood sugar levels. Many brain symptoms are caused by hypoglycemia.”

“The reserves of ATP in cells are very small. At any one moment in heart muscle cells there is only enough ATP to last about ten contractions. Thus the mitochondria have to be extremely good at re-cycling ATP to keep the cell constantly supplied with energy.”

“I actually now believe that a low red cell magnesium is a symptom of mitochondrial failure. It is the job of mitochondria to produce ATP for cell metabolism and about 40% of all mitochondrial output goes into maintaining calcium/magnesium and sodium/potassium ion pumps. I suspect that when mitochondria fail, these pumps malfunction and therefore calcium leaks into cells and magnesium leaks out of cells. This, of course, compounds the underlying mitochondrial failure because calcium is toxic to mitochondria and magnesium is necessary for normal mitochondrial function.”


“Thus, mitochondrial dysfunction resulting in impaired ATP production and recycling is a biologically plausible hypothesis, and there is considerable evidence that it is a contributory factor in CFS...

... The “ATP profile” (test) results indicate mitochondrial dysfunction of the neutrophils in the patients in our cohort, and moreover the degree of dysfunction is strongly correlated with the severity of their illness. Neutrophils are the major effector cells of the immune system and the observed mitochondrial dysfunction is bound to have a deleterious effect on this system.”

CFS is Heart Failure Secondary to Mitochondrial Malfunction by Sarah Myhill,  [Link](#)

“The job of the heart is to maintain blood pressure. If the blood pressure falls, organs start to fail. If the heart is working inadequately as a pump then the only way blood pressure can be sustained is by shutting down blood supply to organs. Organs are shut down in terms of priority, i.e. the skin first, then muscles, followed by liver, gut, brain, etc. As these organ systems shut down, this creates further problems for the body in terms of toxic overload, susceptibility to viruses which damage mitochondria further, thus exacerbating all the problems of the CFS sufferer.”
Mitochondrial Function Test & Chronic Fatigue Syndrome by Dr. Charles Forsyth (2009)

“When mitochondrial function is impaired, all muscle function is impaired and this includes heart (cardiac) muscle. Indeed low cardiac output has already been demonstrated in fatigue syndromes and elegantly explains the symptoms these patients suffer from. For example, they have low blood pressure, marked postural hypotension, low blood volume and perfusion defects. Poor circulation of skin would explain cold hands, cold feet and difficulty with temperature regulation, poor circulation of the brain explains the cerebral symptoms and so on...

... Dr. Arnold Peckerman (SEE BELOW), a cardiologist in America, believes that many of the cardiomyopathies and congestive cardiac failures are not just due to poor blood supply, but poor mitochondrial function... The effect is not confined to muscles – it affects all cells and organs, including brain, liver, kidney, etc.”

The Heart of the Matter: CFS & Cardiac Issues by Carol Sieverling, (2005) Link

“What this very impressive article says is that, without exception, every disabled CFS patient is in heart failure...

... Almost everyone with CFIDS has Compensated Idiopathic Cardiomyopathy...

... The short version is that cardiac muscles have lost power because their mitochondria are dysfunctional. They’re not functioning well because of a redox-state problem.”


“The patients with severe CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. Post-exertional fatigue and flu-like symptoms of infection differentiated the patients with severe CFS from those with less severe CFS and were predictive of lower cardiac output. In contrast, neuropsychiatric symptoms showed no specific association with cardiac output. Conclusion: These results provide a preliminary indication of reduced circulation in patients with severe CFS.”
- **Cardiac Output Linked to Severe CFS Cases** (Interview with Dr. Arnold Peckerman), by Mark Giuliucci, *CFIDS Association of America - The CFS Research Review* (2003) [Link](#)

  "*Many of the symptoms of CFS, such as post-exertional fatigue, are also symptoms of low cardiac output.* A person can have low cardiac output for a number of reasons, but the result is the same — circulation slows down and some organs may not get enough blood flowing through them...

  ... in some patients with CFS, blood pressure is maintained at the cost of restricted flow, possibly resulting in a low flow circulatory state.”

  *Stephen Sinatra MD*

- **Nutritional Interventions to Reduce Cardio-metabolic Risk** by Dr. Stephen Sinatra (Abstract and slides from 2011 American College of Nutrition Presentation) [Link](#)

  "*Gulf War Syndrome, chronic fatigue, migraine headache, mercury toxicity, diastolic dysfunction (DD), statin cardiomyopathy, and likely many other conditions, share a common and overlooked denominator - mitochondrial damage, deterioration, and dysfunction leading to impaired production of adenosine triphosphate (ATP) and an increase in oxidative burden. Multiple studies have demonstrated a strong epidemiological relationship between mitochondrial degeneration and pathology, yet mitochondrial status receives little or no attention in clinical practice.*"


  "*One characteristic of the failing heart is a persistent and progressive loss of cellular energy substrates and abnormalities in cardiac bioenergetics that directly compromise diastolic performance, with the capacity to impact global cardiac function. Cardiologists must learn that the heart is all about ATP, and the bottom line in the treatment of any form of cardiovascular disease, especially congestive heart failure and cardiomyopathy, is restoration of the heart’s energy reserve...*

  ... *Metabolic cardiology describes the biochemical interventions that can be employed to directly improve energy metabolism in heart cells. In simple terms, sick hearts leak out and lose vital ATP, and the endogenous restoration of ATP cannot keep pace with the insidious deficit and relentless depletion. When ATP levels drop, diastolic function – the most important precursor of congestive heart failure deteriorates.*"
**Metabolic Cardiology – It’s All About ATP**, (Interview with Dr. Stephen Sinatra)

“... great amounts of ATP are needed to produce this stream of energy and the cells can’t store this much ATP. Instead cells rely on a constant stream of replenishment of ATP. This is called ATP turnover...

... Anybody with cardiovascular disease– where the heart is compromised in some way - is always leaking ATP...

... Enormous levels of ADP are generated which can’t regenerate back to ATP. Then AMP is formed. With the high levels of AMP, this diffuses out into cytoplasm of the cell...

... The bottom line is that the body can’t make ATP back fast enough by de novo synthesis. De novo synthesis of ATP can take weeks, some researchers say up to 100 days...

...What I have learned as a clinical cardiologist is that it is all about ATP. It’s not about oxygen! Cardiologists are always thinking about oxygen in the heart and oxygen is important but oxygen is only the stepping stone to ATP."

Joanne Ingwall PhD

**Energy Metabolism in Heart Failure and Remodelling**, by Joanne Ingwall,
*Cardiovascular Research*, 81(3):412-419 (2009) [Link](#)

“Because the amount of ATP in the heart is small (~10 mM, enough for only a few beats) compared with demand (as much as 10 000 times greater), the myocardial cell must continually re-synthesize ATP to maintain normal cardiac pump function and cellular viability. Consequently, the rates of ATP utilization and re-synthesis are very large. The concentration of ATP is maintained constant, despite large and variable changes in ATP demand.

ATP re-synthesis by fatty acid oxidation in mitochondria is normally sufficient to meet the dynamic demands for chemical energy and is the primary pathway for ATP synthesis. Under conditions of high ATP demand relative to ATP availability, the myocyte (muscle cell) recruits additional pathways for ATP synthesis, namely glycolysis and the phosphotransferase reactions catalyzed by creatine kinase (CK) and adenylate kinase (AK). The different pathways for ATP supply have different rates of ATP synthesis: phosphoryl transfer via CK is 10 times faster than ATP synthesis in mitochondria, which is 20 times faster than glycolysis.
The relative contributions of these pathways to overall ATP synthesis change rapidly in response to changes in fuel supply, hormonal and neural signals, availability of substrates and inhibitors of specific enzyme reactions, and by chemical modification of proteins. During acute increases in work in the normal myocardium, glycogen is used, more glucose is influxed, and phosphocreatine (PCr), the primary energy reserve compound in the heart) is used to support the demand for more ATP. “

“... it is now known that energy metabolism in myocytes of the failing heart remodels, resulting in a progressive loss of ATP.”

“In uncompensated hypertrophy and in other forms of heart failure, CK flux and fatty acid oxidation are both lower, any increases in glucose uptake and utilization are not sufficient to compensate for overall decreases in the capacity for ATP supply; and [ATP] falls.”


“Studies of experimental and human heart failure have shown that total CK activity, [Cr], and [PCr] are all lower than in normal myocardium. Experiments using animal models in which either CK activity or the Cr content was acutely or chronically reduced have demonstrated that integrity of the CK pathway is necessary to maintain the contractile reserve of the heart. “

“Moreover, [PCr] has been shown to be a predictor of mortality in heart failure patients. Thus, the CK system not only has a functional role maintaining chemical energy needed for ATP-requiring reactions, but also serves as an index of the extent of cardiac pump failure.”


“It is important to emphasize that the energetic state of the heart is not defined simply by the concentration of ATP. The amount of ATP made and used per minute (turnover) is many times greater than the size of the ATP pool. Thus, maintaining a high ATP supply is critically important for maintaining cardiac performance. The ability of the complex metabolic machinery in the heart to oxidize a variety of carbon-based fuels for ATP synthesis ensures that [ATP] remains constant despite varying ATP turnover rates.”
“A recent study using H NMR spectroscopy demonstrated creatine (CK) depletion in human heart failure and, moreover, that the magnitude of the decrease was related to heart failure severity.”

“The evidence amassed to date suggests that the following sequence of events occurs in the progression to myocardial pump failure. [PCr] decreases in hypertrophy and failure because of a mismatch in ATP supply and demand. This is followed by a loss in [creatine] by as much as 60% and by a decrease in [ATP]. The loss of creatine is cardiac specific and is nearly an order of magnitude faster than loss of ATP. ATP slowly and progressively decreases in the dysfunctional and failing myocardium to a lower limit of ≈70% to 75% of normal values.”

“The observation that [ATP] decreases in the failing heart means that the normal well designed well integrated metabolic machinery has failed. Moreover, because the [ATP] poor state persists in the failing heart, the normal mechanisms that slowly replete the ATP pool after myocardial ischemia and infarction must also “fail.” The decrease in [ATP] is important because it signals a massive change in normal metabolic regulation, one that is unable to support normal levels of either ATP or PCr.”

“ATP synthesis by oxidative phosphorylation in the mitochondria is usually sufficient to maintain normal ATP levels even when the workload of the heart changes 3 to 5 fold. The ability of the metabolic machinery in the heart to oxidize a variety of carbon-based fuels for ATP synthesis insures that ATP concentrations remain constant.

Maintaining a constant level of ATP to preserve cell viability and to drive the ATPase reactions during the normal variations in work output is so important that the heart has energy reserve systems. The primary energy reserve compound in the heart is phosphocreatine (PCr) which is present in concentrations twice that of ATP. The enzyme creatine kinase transfers the phosphoryl group between ATP and PCr at a rate 10-times faster than the rate of ATP synthesis by oxidative phosphorylation.”
“An adult human heart has the highest oxygen uptake rate in the body and consumes about 6 kg of adenosine triphosphate (ATP) daily – 15-20 times its own weight – to maintain the daily activities of an individual. Since the cardiac ATP content is <1 gram, cardiac myocytes have to work diligently to match the energy supply to the tremendous demand and, thereby, maintain normal energetics and cardiac function.

Because of its high energy-dependent nature, the heart has developed an extraordinary capacity for energy production. Indeed, the heart features the highest mitochondrial density among all organs; approximately one-third of the cell volume in cardiac myocytes is occupied by mitochondria, in which oxidative metabolism for ATP synthesis occurs. Moreover, the heart is able to utilize a variety of substrates for energy generation, including carbohydrates (glucose and lactate), lipids (free fatty acids and triglycerides), and ketones. These mechanisms allow a normal heart to maintain its functional performance in a wide range of physiological conditions without experiencing an energy debt.

Despite the extraordinary capacity for energy production, failing hearts become energy deprived. This is evident by a significant decrease in the myocardial content of the energy reserve compound, phosphocreatine (PCr), which rapidly regenerates ATP when there is an abrupt increase in energy demand. The decrease in PCr is followed by the eventual depletion of myocardial ATP content during end-stage heart failure. Long-term follow-up studies in patients with idiopathic dilated cardiomyopathy demonstrate that decreased PCr is an independent predictor of mortality, suggesting that impaired myocardial energetics play an active role in the progression