From the Thyroid to the Heart

By Roy Moncayo & Helga Moncayo

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GJMR-K Classification: NLMC Code: WK 200, WG 200

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Abstract- The pathogenesis of human disease is commonly considered to be unique to each organ or system. This has led to specialization in medical practice leaving little space for global pathogenesis concepts. In this review we have departed from a biochemical concept of coenzyme Q10 (CoQ10) deficiency and its relation to the initiation of hypoxia response in a systemic way. Several conditions of secondary CoQ10 deficiency are known in the literature by which the organs involved could be affected by hypoxia and switch to glycolytic metabolism. The most salient biomarkers of this situation are the low T3 syndrome and the elevation of IL-6. These parameters together with CoQ10 deficiency delineate a condition of acquired mitochondrial dysfunction. Additional related biochemical deficiency conditions affect magnesium, selenium, and iron levels. Visualization of glycolysis can be clearly achieved by diagnostic imaging methods based on the use of 18F-fluorodeoxyglucose (18F-FDG). We present several examples of diagnostic imaging with 18F-FDG to demonstrate our model of acquired mitochondrial dysfunction and disease.

I. Introduction

Through a series of observational studies on the pathogenesis of benign thyroid disease we were able to deduce in 2021 that the central pathogenetic mechanism was a condition of glycolytic metabolism as evidenced through combined diagnostic imaging with 3D-power Doppler sonography and positron emission tomography (PET) using 18F-fluorodeoxyglucose (18F-FDG) (Figure 6 in (1)). In the 18F-FDG study both the thyroid and the heart displayed an intense tracer uptake (Figure 1), an association never commented before in the literature (2). Since the innate capability of deoxyglucose is to indicate glycolysis (3), we interpreted the image as an in-vivo depiction of this metabolic process which correlated with increased vascularity. Given that patients with benign thyroid disease frequently have low levels of coenzyme Q10 (CoQ10) and that experimental CoQ10 deficiency is linked to hypoxia as shown by Liparulo et al., in 2021 (4), our current interpretation of the diagnostic image shown below is that it represents glycolysis and is related to conditions of hypoxia. In Liparulo’s experiment with the human T67 glioma cell line, CoQ10 deficiency was produced by inhibiting its biosynthesis using the competitive inhibitor 4-nitrobenzoate leading finally to low intracellular levels of oxygen, i.e., hypoxia (4).

Figure 1: 18F-FDG PET Study of a Patient with Recurrent Active Thyroiditis. Intense Tracer Uptake is Seen in the Thyroid and the Heart. The Brain Shows a Physiological Uptake. The renal pelvis, the ureters, and the urinary bladder Depict the Physiological Excretion Path. Panel B Shows the Simple Pathogenetic Mechanism Leading to Hypoxia.

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Our previous experience with CoQ_{10} deficiency had shown that this condition is reversible when CoQ_{10} supplementation at a dose of 0.9mg/kg body weight combined with magnesium citrate 2400mg/d, and selenium 200µg/d was given. This reversibility can be demonstrated by the restitution of normal perfusion and morphology of the thyroid (5). The clinical investigation of our patients was based on a conceptual model of coordinated interactions between magnesium, selenium, iron, and CoQ_{10} as they relate to mitochondrial function (Figure 2). The clinical impact of these processes has been discussed elsewhere (1, 5-11).

The main messages from Figure 2 include: 1) daily life and physical stressors can lead to magnesium deficiency (12, 13) which will affect iodine and selenium uptake and thyroid hormone formation (14-16). 2) Selenium deficiency (7) will affect the anti-oxidative protection of the body by altering selenoprotein synthesis (17, 18) and altered activation of CoQ_{10} to ubiquinol through thioredoxin reductase (19), potentiating oxidative damage. One fact that is often overlooked is that CoQ_{10} has a positive correlation to selenium levels (20). 3) A decrease of magnesium availability will affect primarily the production of ATP from Mg-ADP (21) as well as the uptake of selenium. 4) The lack of ATP will alter the function of the unfolded protein response of the endoplasmic reticulum (22). Iron deficiency affects thyroid peroxidase (23), mitochondrial iron sulfur clusters (24, 25), and regulation of HIF through prolyl hydroxylases.

To demonstrate the concept of CoQ_{10} deficiency we will first review basic concepts on the substance and add an introduction on diagnostic imaging procedures based primarily on the use of ¹⁸F-FDG.

Nuclear Medicine diagnostic imaging based on the use of ¹⁸F-FDG PET has been primarily considered as a diagnostic method for oncological work (26).
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rat her restrictive notion emerged during the early years of clinical use of $^{18}$F-FDG when tracer availability and imaging capacity at specialized institutions were limited (26). Disregarding these conceptual and practical limitations, in 2003 we applied the methodology for the diagnosis of arteritis (27). Visualization of fatty acid oxidation can be achieved using the specific tracer [123I]-$\beta$-Methyl iodophenyl-pentadecanoic acid (BMIPP) (28, 29). The beta oxidation of free fatty acids constitutes the primary source of energy and ATP production in the heart (30). Once the oxidation of free fatty acids is diminished, glycolysis takes over in the failing heart (31). This is accompanied by increased glycolytic metabolism. Figure 3 shows summarily mechanisms of CoQ$_{10}$ deficiency and their relation to metabolism and Nuclear Medicine diagnostic imaging.

Figure 3: General changes of mitochondrial metabolism and systemic parameters under hypoxia.

a) Basic notes on coenzyme Q$_{10}$

The first description of coenzyme Q$_{10}$ (CoQ$_{10}$) was done by Festenstein in 1955 who was working on the general topic of quinones (32). CoQ$_{10}$ is a small lipophilic molecule located widely in cell membranes. Due to its distribution, it was named ubiquitous quinone. Beginning in 1957 Crane and coworkers published a series of studies on the characterization of CoQ$_{10}$. An early publication dealt with the isolation of a quinone from the mitochondria of beef heart. The authors described the capability of the compound to undergo oxidation and reduction in a reversible way. The denomination Q-275 for CoQ$_{10}$ was derived from the absorption spectrum of the substance (33). Different compounds having quinone structure have been described in different species (34). In 1959 CoQ$_{10}$ and the succinoxidase activity of the electron transport system were studied by Crane (35) as well as by Hendlin and Cook in 1960 (36). The structure of CoQ$_{10}$ characterized as a 2,3-dimethoxy benzoquinone structure was published by Wolf et al., in 1958 (37).

The biochemical characteristics of quinones were summarized by Hoffmann-Ostenhof in 1947 (38). In 1948 Friedmann, Marrian, and Simonreuss described the antimitotic effects of quinones in relation to their structure (39). Further information on the biochemistry of quinones was published by Barnes in 1963 (Section 3 in (40)).

Gale et al., evaluated the mean content of CoQ$_{10}$ in different human organs in 1961 (41) showing that the brain and thyroid have the lowest concentrations (Figure 2).

Due to frequent incidence of thyroid disease in the general population, we hypothesize that organs with higher levels of CoQ$_{10}$ can be more resistant to alteration and retain function. The thyroid would be at the end of the scale.
The relations between the organ content of CoQ$_{10}$ or ubiquinone and age have been studied by Kalén, Appelkvist, and Dallner in 1989 (42). An abridged summary of their data is shown in Table 1. The highest levels are found in the age group 19-21 years while older subjects have lower levels.

### Table 1: CoQ$_{10}$ levels in selected organs according to age (extracted from (42)).

<table>
<thead>
<tr>
<th>Age</th>
<th>Ubiquinone µg/d ww</th>
<th>CoQ$_{10}$ mg/100g Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7 - 2 years</td>
<td>1-3 days</td>
<td>0.7 - 2</td>
</tr>
<tr>
<td>Heart</td>
<td>36.7</td>
<td>78.5</td>
</tr>
<tr>
<td>Kidney</td>
<td>17.4</td>
<td>53.4</td>
</tr>
<tr>
<td>Liver</td>
<td>12.9</td>
<td>45.1</td>
</tr>
<tr>
<td>19 - 21 years</td>
<td>19 - 21 years</td>
<td>19 - 21</td>
</tr>
<tr>
<td>Heart</td>
<td>110.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>98.0</td>
<td>71.1</td>
</tr>
<tr>
<td>Liver</td>
<td>61.2</td>
<td>58.3</td>
</tr>
<tr>
<td>39 - 43 years</td>
<td>39 - 43 years</td>
<td>39 - 43</td>
</tr>
<tr>
<td>Heart</td>
<td>47.2</td>
<td>75.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>64.0</td>
<td>71.1</td>
</tr>
<tr>
<td>Liver</td>
<td>50.8</td>
<td>58.3</td>
</tr>
<tr>
<td>77 - 81 years</td>
<td>77 - 81 years</td>
<td>77 - 81</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td>47.2</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td>64.0</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>50.8</td>
</tr>
</tbody>
</table>

In 1996 Ravaglia et al., evaluated the correlation of CoQ$_{10}$ levels with body composition and found that levels decreased in a parallel form as did the fat-free body mass and speculated that this diminution would affect muscle performance (43).

Basic information on the pharmacokinetics of CoQ$_{10}$ can be found in the study by Tomono et al., who used a deuterium labeled molecule (44). A first peak in blood was seen at 6 hours, and the half-life was found to be 33 hours. Data on PET tracer biodistribution studies using $^{11}$C-labeled CoQ$_{10}$ and $^{11}$C-ubiquinol were reported by Watanabe et al., in 2019 (45). We have interpolated and summarized their results in Table 2.

### Table 2: Biodistribution of $^{11}$C-labeled CoQ$_{10}$ and ubiquinol (45).

<table>
<thead>
<tr>
<th>CoQ$_{10}$distribution</th>
<th>Ubiquinol2 % ID/g</th>
<th>Ubiquinone2 % ID/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Liver</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Blood</td>
<td>1.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>0.038</td>
<td>0.026</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.04</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Bentinger et al. published a study on the content of CoQ$_{10}$ in endocrine organs (46). Table 1 of this publication shows the high uptake of dietary CoQ$_{10}$ in steroid producing cells such as adrenal cells and ovaries while the thyroid had a much lower uptake.
b) Oxidative processes, selenium, and CoQ\textsubscript{10}

Several investigators have evaluated the effect of external radiation and oxygen toxicity on biological systems since the 1940s. The biological extent of life has been proposed to be associated with concepts of cellular damage due to oxidative processes that produced reaction intermediates originating from unpaired electrons (47). In 1954 Gerschman et al., studied the topic of oxygen poisoning as well as x-irradiation proposing a common mechanism which was related to the oxidizing free radicals (48). In 1955 Harman published a theory of aging by describing deleterious effects arising from injuries due to free radicals (49). These investigations as well as those of Ritossa on the changes caused by heat shock (50), had in common an external component which was acting as a pathogenic factor affecting living cells ending with oxidative changes.

Early investigations on selenium addressed its role in liver disease. In 1957 Schwarz and Foltz (51) described the beneficial effect of selenium in the context of dietary necrotic liver degeneration. They identified selenium in a fraction originally called Factor 3. Modern research has described the complex array of selenoproteins with antioxidant functions including glutathione peroxidase (52-54).

We have chosen to consider selenium and CoQ\textsubscript{10} together based on observations made by Green et al., in 1961 (55) and by Hidioglu in 1967 (56) who found a close functional relation between both substances such that selenium administration improved the tissue levels of CoQ\textsubscript{10} in experimental animals. Vadhanavikit and Ganther published similar observations in 1993 and 1994 (57, 58). The authors speculated that lowering of CoQ\textsubscript{10} levels depended on the depressed activity of GSH-Px which was the consequence of selenium deficiency (58). This finding implies that hypoxia can develop starting from selenium deficiency which then affects CoQ\textsubscript{10} levels. Unfortunately, this important physiological connection has not been considered in many studies. Putting the focus only on one of these elements in the context of supplementation have remained inconclusive (59-61).

On the other hand, specific single mechanisms can be indeed characterized.

Ernster and Formark-André described the anti-oxidant actions of ubiquinol, i.e. the reduced form of CoQ\textsubscript{10}, in aerobic organisms (62). Sugiyama studied the anti-oxidative effect of CoQ\textsubscript{10} administering a dose of 2mg/k which is equivalent to \(~\)140 mg for an adult with 70 k body weight. Both the in-vivo experiments as well as the in-vitro studies demonstrated that under CoQ\textsubscript{10} lipo-peroxides were significantly lower as compared to the controls (Table 1 in (63)). Degli Esposti et al. characterized the functional role of CoQ\textsubscript{10} in Complex I of the OXPHOS chain emphasizing its energetic function (64). In 2017 Shimizu et al. described an association between low CoQ\textsubscript{10} levels and hospital mortality in patients with cardiac disease (65). Heart arrest patients also shared this feature of having very low levels of CoQ\textsubscript{10} (66).

Under experimental conditions the administration of selenium compounds has resulted in inhibition of angiogenesis as well as of VEGF expression (67, 68). In our studies we have observed a similar action for CoQ\textsubscript{10} (5). We propose that these actions add a positive effect to counteract changes due to hypoxia.

c) Warburg and the development of 2-desoxy-D-glucose

The theory behind the development of 2-desoxy-D-glucose can be traced back indirectly to the work of Otto Warburg. In 1911 he carried out experiments with the sea urchin (Arbacia pustulosa) and with nucleated avian erythrocytes (69). The blood cells had been exposed to low temperatures between -15° and -20° C to freeze them. The frozen material was then exposed to 38° C to break the cells. This handling produced a temperature increase of approximately 60°C. The resultant experimental acellular material was a dark liquid. Oxygen consumption in the material won from younger blood cells was higher than in intact red blood cells. A closer analysis of the 1923 publication by Warburg and Minami clearly showed the influence of raised temperature (70). These experiments were unknowingly ahead of time to those on the heat shock response done in 1962 by Ritossa where heat shock was produced by setting the temperature to 30°C for thirty minutes (50). Warburg’s experiments have never been interpreted in the context of the heat shock (71-74) nor of endoplasmic reticulum stress (75). Endoplasmic reticulum stress is a logical consequence since heat shock will produce protein aggregation (76). Experimental heat shock can induce glycolysis to compensate ATP balance (77) and activate the endoplasmic reticulum stress response mechanisms (78).

In 1928 Warburg published “The metabolism of tumors in the body” (79) where he described the metabolic characteristics of 2 tumor models, Flexner-Jobling’s rat carcinoma (80), and Jensen’s rat sarcoma (81). In their experiment they measured the glucose content in in-going and out-going tumor vessels. The average values in the experiments with the Jensen sarcoma substrate revealed a mean glucose concentration of 124 mg % in the arterial vessels, and 54 mg % in the venous vessel (Table II in (79)). On the other hand lactic acid in the tumor cavity was higher than in the aorta by 69 mg% (Table V in (79)).

In 1922 Bergmann, Schotte, and Lechinsky published their work on the development of deoxyglucose as an antagonist of glycolysis and added experimental data aimed at elucidating the reactivity of glucosides after introducing structural changes at the
C2 position of the glucose molecule (82). Further experimental work on deoxy-glucose as an antagonist of glycolysis was published by Francis B. Cramer and Gladys Woodward in 1952 (3, 83-85). They showed a reduction of approximately 60% of glucose metabolism under anaerobic conditions working with slices of Walker 256 rat carcinoma samples when an equimolar quantity of 2-deoxy-D-glucose was added. The Walker 256 rat carcinoma originated in 1928 from a mammary gland tumor of a pregnant rat (page 261 in (86)). Confirmation of the avidity of Walker-256 tumor cells for 18F-FDG was provided in 2019 by Li et al. (Figure 2 in (87)).

Woodward and Cramer (3) included only two literature references in their publication: their previous work and a 1930 translation of Warburg’s previous work (88). The word “relation” was used to connect the content of both publications.

In 1957 Wick et al. described the primary metabolic block on glucose that 2-deoxyglucose produces (89). In 1961 Barban described this mechanism as follows: “... inhibits glycolysis and growth of cultured human cells” (page 1890 in (90)). These results clearly associated 2-deoxyglucose with glycolysis. With the development of 18F-labelled deoxyglucose by Som in 1980, a diagnostic tool for glycolysis imaging became available (91).

d) Narrative description of hypoxia and cardiac metabolism

Hypoxia stands for a biochemical state where oxygen availability is limited. According to Richalet in “The Invention of Hypoxia”, the term appeared in the literature about 1909 in a publication originating from Germany (92). At this time Joseph Barcroft published two studies dealing with the consequences of insufficient oxygen supply to the body. In 1908 he presented a review of the scientific evidence known up to that time (93). In 1920 he discussed the consequences of insufficient oxygen supply as follows: “The statement has been made that “anoxaemia not only stops the machine, but wrecks the machinery” (94). In modern times we can interpret this statement as suggesting multi-organ failure (95).

In 1964 Nunn and Freeman discussed that tissue hypoxia can arise from hemorrhagic shock 1964 (96). In 1969 Henderson (97) and McDowall (98) presented summaries of the biochemical concepts of hypoxia which appeared in the British Journal of Anesthesiology. In 1977 Alberti discussed the consequences of hypoxia on biochemical terms. Equation 11 of this publication identified the role of CoQ10 in the synthesis of ATP (99).

In 1987 Bihari discussed the relation of hypoxia to septic shock (100). Some biochemical characteristics of hypoxia were described by Webster in 1987 who reported the relation between hypoxia and activation of glycolysis (101).

In 1988 Goldberg, Dunning, and Bunn characterized the oxygen sensing function as being associated with heme protein (102). In 1992 Loike et al. showed that when endothelial cells were exposed to hypoxia an upregulation of glucose transport could be observed (103). At a cellular level, the metabolic consequences of hypoxia include diminution of fatty acid oxidation and activation of glycolysis (Figure 1 in (104)) as well as an increased expression of interleukin 6 (105).

The transcriptional adaptation to experimental hypoxia was characterized in 1993 by Wang and Semenza defining a role for the hypoxia inducible factor 1 (HIF-1α) using hepatoma tumor cells (Hep3B) (106). In 1999 Ouddir et al. demonstrated that the expression of the glucose transporter in alveolar epithelial cells could be upregulated by hypoxia. In their experiments this was reflected by increased uptake of deoxyglucose (Figure 2 in (107)) which is connected to increased glycolysis.

In 2010 Solaini et al. described major changes in mitochondria found in hypoxia. Figure 1 depicted a connection between hypoxia and diminished electron transport and increased ROS production. The authors conceived these changes as stabilizing factors of HIF (108). Lee, Chandel, and Simon discussed mechanisms of cellular changes following hypoxia adding the involvement of endoplasmic reticulum stress and of the unfolded protein response (Figure 2 in (109)).

Recent reviews on hypoxia research have been published by Thompson in 2016 (110) as well as by Luo et al. in 2022. Luo’s publication included an informative pictorial summary of relevant landmarks (111). Kierans and Taylor idealized that increased glycolysis was the event that goes directly from hypoxia to HIF-1α expression ending with the expression of enzymes involved in glycolysis (112). Della Rocca and coworkers summarized clinical data on diseases related to hypoxia in 2022 (113).

The beta oxidation of free fatty acids constitutes the primary source of energy and ATP production in the heart (30). Tatem and coworkers have demonstrated that myocardial infarction patients show a diminished utilization of free fatty acids which did not correlate with the findings of myocardial perfusion (114). Changes in cardiac fatty acid utilization show a dynamic course as reported by Zen et al., (115). Biswas et al., demonstrated lower BMIPP uptake following acute infarction of the myocardium (116) as well as a negative correlation between left ventricular ejection fraction and tracer wash out rate. They also described a positive correlation between washout rate of BMIPP and blood level of NT-proBNP (Figures 4 and 5, respectively in (117)).
The graphical appearance of decreased BMIPP uptake as seen in planar images was shown in Figure 6 by Biswas. Increasing levels of NT-proBNP, a biomarker of heart failure (118), correlated positively with an increased wash-out rate of BMIPP (Figure 5 in (119)) as well as a higher incidence of cardiac events when cardiac tracer uptake was low (Figure 6 in (119)).

Figure 6: CoQ$_{10}$ levels in relation to stressors. Taken from Boreková M, Höjerová J, Koprda V, Bauerová K. Nourishing and Health Benefits of Coenzyme Q10. Czech J Food Sci (2008) 26(4): 229-41. doi: https://doi.org/10.17221/1122-CJFS. License CC BY NC 4.0

Low levels of CoQ$_{10}$ have been found in children who presented food allergies (121). The same applied to acute influenza (122). A similar situation can be found in patients after cardiac arrest as well as septic patients (66, 123) and in critical illness (124). Studies on postoperative follow-up have shown indirectly that surgery induces a decrease of CoQ$_{10}$ levels. This drop can be prevented by supplementation with CoQ$_{10}$ (125).

Experimental studies done by Fischer et al., have shown alterations in CoQ$_{10}$ levels after dietary restriction (126). Experimental burns can lead to mitochondrial damage and dysfunction and can be corrected by CoQ$_{10}$ administration (127). Similar observations have been published by Xu et al., relating CoQ$_{10}$ administration to protection against myocardial cell changes induced by heat stress (128, 129).

Experimental hypoxia in skeletal muscle of rabbits is accompanied by a reduction of the levels of ubiquinone (130). A decrease of the CoQ$_{10}$ levels goes along with low ATP levels in isolated rabbit ventricles under hypoxia (Table 2 in (131)).

The administration of antineoplastic antibiotics such as adriamycin can inhibit the synthesis of CoQ$_{10}$ (132). This interference could arise from the similar quinone structure of both CoQ$_{10}$ and adriamycin (133-138). A further effect of this inhibition is the decrease of free fatty acid oxidation. In 2000 and 2003, Saito et al. demonstrated that cardiac BMIPP uptake was decreased after doxorubicin (139) and taxan (140) administration. On the other hand, it has been shown that doxorubicin cardiotoxicity can be prevented by administration of CoQ$_{10}$ (141). Bradamante et al. considered hypoxia to be a risk factor for doxorubicin-induced cardiotoxicity (142). Muhammed, Rama sarma, and Kurup described in 1983 that adriamycin inhibited oxidative phosphorylation in freshly prepared mitochondria (135).

In 2013 Umezawa et al., demonstrated that external radiation therapy affected BMIPP uptake. The irradiated area of the heart (red arrows in Figure 4) showed no tracer uptake (143). Although the CoQ$_{10}$ levels were not evaluated, the image pattern is highly suggestive of induced CoQ$_{10}$ deficiency. In a subsequent publication the authors described a relation between the radiation dose applied and the degree of BMIPP alteration (144).
Following the concept of metabolic switch from free fatty oxidation to glycolysis, Yan et al., have demonstrated that radiation-induced changes in myocardial metabolism are accompanied by a high uptake of $^{18}$F-FDG (Figures 2 and 3 in (145)), thus reflecting glycolysis.

A series of studies have demonstrated that altered free fatty acid oxidation can be restituted by administrating the ACE-inhibitor enalapril (146-150) (Figure 5).

Clinical situations associated with diminished BMIPP uptake

The uptake mechanism of free fatty acids requires a transport system that involves the CD36 molecule. When there is a deficiency of this structure, $^{18}$F-FDG uptake has been shown to be increased. This alteration can be corrected by administrating carvedilol (151) (Figure 6).
Dilated Cardiomyopathy With CD36 Deficiency

The complementary situation, i.e., diminished free fatty oxidation, can be found in patients with CD36 deficiency. Nishimura demonstrated that subjects with CD36 deficiency and cardiomyopathy had low BMIPP uptake. This defect could be corrected by the administration of CoQ₁₀ using a dose of 30mg/d for 35 days (152) (Figure 7).

**Figure 6:** Taken from Hirooka et al. (151). Hirooka K, Yasumura Y, Ishida Y, Komamura K, Hanatani A, Nakatani S, et al. Improvement in Cardiac Function and Free Fatty Acid Metabolism in a Case of Dilated Cardiomyopathy with Cd36 Deficiency. Jpn Circ J (2000) 64(9): 731-5. doi: https://doi.org/10.1253/jcj.64.731. License granted

The images presented above demonstrate the ability of Nuclear Medicine to reveal the metabolic situation of the heart. Besides the therapeutic use of CoQ10, enalapril administration has also led to normalization of BMIPP defects. This supports the clinical value of enalapril in the treatment of patients with heart failure with reduced cardiac function (153). The data suggest that there is a restitution of normal oxidative phosphorylation (154-156).

Alba Timón-Gómez, and Antoni Barrientos have summarized data on changes of the functional status of mitochondrial Complex I from active to dormant under hypoxia (157). In addition to this the microRNA molecule miR-210 has been found to be involved in these changes.

Inhibition of NDUFS, NDUFA4, and NDUFA4L2 affect also Complex I and Complex IV (Figure 1 in (157)). NDUFS is the mitochondrial NADH-ubiquinone oxidoreductase 75 kDa subunit and NDUFA corresponds to NADH:ubiquinone oxidoreductase subunit A. Alterations of these molecules affect the function of Complex I.

The scientific literature contains scarce information about CoQ10 and hypoxia in human disease. Hypoxemia is a recognized problem associated with congenital heart disease (158), and with viral infections (Figure 2 in (159), Figure 2 in (160)). The role of hypoxia in chronic kidney disease has been discussed by Wang et al., (161). Chen et al., depicted the progression of kidney disease linking hypoxia and fibrosis (Figure 4 in (162)). Hypoxia in the context of COVID-19 has been recently summarized by Østergaard in 2022 setting a focus on capillary changes (163).

The condition of chronic hypoxemia is associated with diminished cardiac function and low levels of ATP (164). Morita et al. described the beneficial effect of CoQ10 in an experimental model of hypoxemia-reoxygenation injury done with heart tissue homogenates (164).

Recent studies on the rare disease Moyamoya have revealed some single possible similarities to the changes we have found in patients with thyroid disease. These findings include excessive collateral vessels and elevated VEGF levels (165), expression of HIF-1 and TGF-beta in the endothelium (166) as well as specific vascular changes (167). In 2022 Ma et al., described that the blood levels of CoQ10 in this rare disease were significantly lower as compared to controls (168).

The selective evolution of mitochondrial diversity has been described as a central element for cell type-specific expression (Figure 1 in (169)). A recent statistical meta-analysis has added information on the polymorphisms of the hypoxia-inducible factor 1-alpha gene finding specific associations with different entities such as cardiovascular disease, skin disease, COPD, and complications of diabetes (170). Following stabilization of HIF there is a downstream signaling activation in several organs (171). This finding tells us that hypoxia has different phenotypes.

Clinical conditions and biochemical features associated with hypoxia

Figure 8 shows our theoretical abstraction of biochemical processes arising from hypoxia where we place CoQ10 deficiency as a key central element. In the following sections we will describe the biochemical changes associated with hypoxia such as the the low T3 syndrome and elevation of interleukin-6 (IL-6) levels.
h) Hypoxia and the low T3 syndrome – a causal path?

The low T3 syndrome or euthyroid sick syndrome has been described by several authors as being associated with many different conditions. In 1974 decreased levels of total triiodothyronine were observed in patients with chronic liver disease, chronic obstructive lung disease, chronic renal failure, and intensive care situations. The authors attributed these changes to lower production of TRH following stress or undernutrition (172). A review on the euthyroid sick syndrome by Wartofsky and Burman published 1982 mentioned possible endocrine mechanisms behind this condition. In Table 2 they listed fasting, anorexia nervosa, and protein-calorie malnutrition as conditions that presented the low T3 situation. Many other factors related to the low T3 syndrome can be found in this review. One interesting postulate was that this condition is related to energy conservation by reducing catabolism (173).

In 1983 Vitek, Shatney, Lang, and Cowley studied the time relation between induction of hemorrhagic shock in dogs and changes in the level of thyroid hormones. They described lower levels of T3 and T4 after 20 minutes of shock. A similar situation was described in 3 patients with trauma or shock. The authors interpreted the changes as belonging to the euthyroid sick syndrome (174). In the late 1990s, several investigators had observed changes of thyroid function parameters in relation to severe illness (172), systemic illness (173), and aging (175). This last study by Schroffner considered the low T3 syndrome to be quite frequent in different clinical conditions (175). The mechanisms leading to this condition were described as reduced activation of T4 (176), and as increased degradation of thyroid hormone in septic shock patients (177). In 1980, Moshang et al. reported that hypoxia affected thyroid function parameters (178). Also in 1980, Becker et al., described low levels of triiodothyronine in patients who had suffered thermal injuries (179). In 1990 Sawhney, and Malhotra had demonstrated that hypoxia was related to low levels of thyroid hormones (Figure 1 in (180)).

In 2001 Ross and Petros reviewed the euthyroid sick syndrome in pediatric cardiac patients including those treated at the intensive care unit (181). The authors discussed three potential settings in this situation: adaptive reduction of the metabolic rate, contributor to the disease, of simply due to the severity of illness (181). Table 2 included potential triggers, however hypoxia was not included.

In 2003 Iervasi et al. found that the low T3 syndrome had a prognostic relevance predicting fatal outcome in cardiac patients. The authors evaluated the data from 1058 patients seen at a National Council...
Research Institute of Clinical Physiology in Pisa in 1999 (182). The authors expressed doubt as to whether changed thyroid metabolism had contributed to impairment of heart function.

In 2007 Adler and Wartofsky reviewed the euthyroid sick syndrome and considered it to represent an adaptation to several clinical conditions (183).

An important mechanistic finding relating thyroid hormone metabolism to hypoxia was described in 2008 by Simonides et al. In their study HIf interacted with thyroid hormone deiodinases leading to the low T3 syndrome (184). Their study was based on a previous observation that transforming growth factor beta, a target for HIf, could promote thyroid hormone inactivation (185). This process resulted in lower levels of T3, which are the key feature of the low-T3 syndrome. Considering that deiodinases are selenoproteins (186, 187) and that our model of acquired mitochondrial dysfunction includes selenium deficiency (10, 11), we must add that selenium deficiency must be quite severe to affect the deiodinase system (188). The study by Fraczek-Jucha et al., demonstrated that selenium deficiency does not correlate with the low T3 condition. Their study found a significant association between low T3 and elevated NT-proBNP levels (Table 2 in (189)). Elevated levels of NT-proBNP correlate with diminished dysfunction of the left ventricle in cardiac disease patients (190).

The low T3 syndrome has been found to show an inverse correlation with coronary artery disease (191) as well as with elevated blood levels of NT-proBNP (192, 193).

Bolen et al., described an association of low T3 syndrome with elevated levels of IL-6 (194). In a clinical study with patients that had presented an acute coronary syndrome, Brozaitiene et al., found an association between mortality and low T3 levels as well as with elevated values of NT-proBNP (195). Minai analyzed the data from 625 heart failure patients in 2021 and found that low T3 and NT-proBNP showed an inverse correlation (196).

Many publications hypothesize that changes leading to the low T3 syndrome arise from the thyroid (Figure 1 in (197)) or from the heart in patients with heart disease (Figure 5 in (198)). The incidence of the low T3 syndrome in patients with congestive heart failure has been called “unexpectedly high” (199).

Biegelmeyer et al., reported that low T3 levels are prevalent among non-critically ill patients and that they are predictive of 30-day hospital mortality (200). Cerillo added an observation as to the relation between low T3 and decreased cardiac output in patients scheduled for coronary bypass surgery (201). Abdu et al. reported a higher incidence of cardiac events in patients with MINOCA (Figure 1 in) (202).

A review published by Langouche, Jacobs, and Van den Berghe in 2019 described the appearance of the nonthyroidal illness syndrome across all ages. The authors added a comment as to the still unknown causality of the disease (203).

i) Sepsis and critical illness

Several investigations on the metabolism of sepsis by L’Her, and Sebert have described an environment of altered mitochondrial function where oxygen utilization and Complex I function are affected (204, 205) stating: “Energy- metabolism disturbances during sepsis are characterized by enhanced glycolytic fluxes and reduced mitochondrial respiration. However, it is not known whether these abnormalities are the result of a specific mitochondrial alteration, decreased pyruvate dehydrogenase (PDH) complex activity, depletion of ubiquinone (CoQ10), electron donor for the mitochondrial complex III, or all 3”.

Low levels of CoQ10 have been described in patients with sepsis (123). He et al., conducted a study on pediatric sepsis evaluating levels of CoQ10 as well as the activity of Complex I and III. They found that low levels of these parameters were associated with mortality in children affected by sepsis (206).

Vassiliou et al., reported that septic patients in a critical condition had low levels of CoQ10 (207). Coppadoro et al., described that low levels of CoQ10 are found in a broad range of critically ill patients (124).

Abitagaoglu et al., reported carried out an experimental study on the effect of CoQ10 administration in sepsis. They found that multi-organ involvement of the heart, kidney, and spleen, was decreased under this treatment (208). Soltani et al., carried out a clinical study on the effect of CoQ10 in sepsis and found a positive effect on clinical parameters and mitochondrial function (209). In 2001 Fink advanced the notion of cytopathic hypoxia as a mechanism of disease (210). In 2002 Brealey et al., discussed the association between outcome of septic shock and mitochondrial dysfunction (211). Cornu et al., evaluated the prognostic value of low T3 syndrome in patients with septic shock and found an association with high mortality (212).

j) Energetics and physical exercise: nutritional theories vs. 18F-FDG imaging

Several publications dealing with nutritional theories and energetics have a common element, i.e., the so-called reference man. The original publication on the reference man from 1974 (ICRP 23) corresponds to a description of the chemical composition of the body, the mass of the organs, as well as to data on physiology (213). This publication originated from the need to respond to concerns about the medical effects of ionizing radiation. The International Commission on Radiological Protection was founded in 1928 at the second International Congress of Radiology (ICRP). It is obvious, that energy intake analysis was not the primary worry of the ICRP. Section B of the publication deals with Energy Expenditure stating that food and oxygen
are used according to energy requirements. Oxygen was described together with the process of combustion. Section B7 described energy requirement arising during pregnancy and lactation showing that these conditions require a higher level of energy. The ICRP 23 publication was followed by ICRP 89 in 2002 which was again dedicated to workers dealing with radiation protection (214).

The concept of energetics in the field of ecology does not include biochemical parameters in relation to function (Figure 1 in (215)). In the field of life history research, the economics model discussed by Pontzer and McGrosky mentions metabolic energy as being involved, however the publication contains no evidence as to how energy can be generated in the mitochondria (216). One important aspect included in Life History Theory is that of trade-off between survival and reproduction (217) as well as resource allocation (218). An example of this philosophy can be taken from Jasińska, who described suppressed ovarian function in relation to physical work (219). This concept is closer to general physiology since it considers at least 2 bodily functions while conventional medical physiology picks out single players, e.g., the heart, the thyroid, or human reproduction. It should be noted that classical research on resilience also lacks the inclusion of basic biochemical processes (220, 221).

Energetics changes occurring during lactation have been described since decades. Bauman and Currie discussed a process of nutrient partitioning in 1980 (222). Mowry et al. described metabolic changes aimed at increasing mitochondrial efficiency in relation to reproduction (223). Energetics and fatigue in sports have been described as being related to brain and body functions (224). The theory launched by St. Clair Gibson, Swart, and Tucker has little connection to biochemistry. Their model idealizes a competitive homeostasis system that involves psychological and physiological elements without mentioning mitochondrial function.

Lavin et al., discussed the spectrum of adaptations to exercise at a molecular level putting the item physiological resilience on top (Figure 3 in (225)). Their definition or resilience states “resilience (i.e., ability to tolerate and recover from stressors)” (Page 11 in (225)).

In a previous publication we launched a concept of shared resources as being the central event related to health and disease. When the level of resources is sufficient, survival is assured resulting in resilience. Unbalanced levels of resources are connected to disease (Figure 12 in (1)). Elements of organ function as well as the so-called psychosomatic components of life can be traced down to specific biochemical parameters where magnesium deficiency plays a central role (9).

Mitochondrial function and the generation of ATP via oxidative phosphorylation constitute a central biochemical element in physiology. This function was summarily described by Brand, Orr, Perevoshchikova, and Quinlan in 2013 (226) stating that ATP generation results from the energy release after nutrients have been oxidized (Box 1).

The classic role of mitochondria is oxidative phosphorylation, which generates ATP by utilizing the energy released during the oxidation of the food we eat. ATP is used in turn as the primary energy source for most biochemical and physiological processes, such as growth, movement and homeostasis.

**Box 1:** Role of oxidative phosphorylation in relation to food. Adapted from (226)

The topic of mitochondrial adaptation to nutrient availability was addressed by Liesa and Shirihai in 2013 (227). In 2022 Kyriazis et al., described processes of mitochondrial adaptation to changes in diet (Figure 5 in (228)). The simplistic idea that dietary evaluations and simple calory counting reflect the level of energetics in the body contradict this physiological principle. Anorexia nervosa represents a condition of severe nutritional alteration. It has been included in the list of diseases associated with low-T3 syndrome (173). Niklowitz et al., described signs of CoQ10 depletion in patients with anorexia nervosa (229).

A similar situation can be found in the setting of physical exercise. Loucks and Callister published a study that combined energy cost and exercise intensity in 1993 (230). They showed that the low T3 condition occurred in amenorrhoeic women under energy limitation. They concluded that exercise could have compromised energy availability. Low energy availability is a term used frequently in relation with physical exercise. Slater, Brown, Mc Lay-Cooke, and Black evaluated this aspect in exercising subjects (231). Loucks discussed the role of energy availability in relation to reproductive disruption in 2003 (232).

In the field of sports physiology, the term “Relative Energy Deficiency in Sport (RED- S)” is being used currently. A recent review on this topic published by Cabre et al. in 2022 insisted on the concept of energy availability in terms of kcal/kg (Figure 1 in (233)). The publication does not include any biochemical data as to how the body can use this apparent energy supply (Table 2 in (233)). This simplified model contrasts sharply with the biochemical adaptation of mitochondrial respiration responding to energetic needs and nutrient availability as described by Bennett, Latorre-Muro, and Puigserver (Figure 2 in (234)). We have taken the
Following our line of thought on hypoxia we would like to add data related to exercise. Exercising subjects can develop hypoxemia (235, 236) and physical activity can lead to HIF activation in skeletal muscle (237). Experimental hypoxia in skeletal muscle of rabbits is accompanied by a reduction of the levels of ubiquinone (130). A decrease of the CoQ₁₀ levels is seen together with diminished ATP levels in isolated rabbit ventricles under hypoxia (Table 2 in (131)). Metabolic changes related to exercise can be seen with diagnostic ¹⁸F-FDG imaging. Nakase et al., demonstrated focal uptake in football players (238) (Figure 9).


Tracer uptake can be more intense according to the intensity of exercise such as weightlifting as shown by Yoshimizu et al., in 2022 (239). Not only the muscle involved in weightlifting but also the heart showed intense tracer uptake (figure 10) revealing the systemic dimension of exercise.
COVID-19: the low T3 syndrome, IL-6, and 18F-FDG imaging

Zou et al., evaluated the data from 149 COVID-19 patients in 2020 looking for the characteristics of the low T3 syndrome, which was indeed found in forty-one cases. Disease severity and parameters of inflammation were significantly associated with the changes of thyroid parameters (240). The low T3 syndrome is an indicator of poor prognosis and mortality in COVID-19 patients (241). The low T3 syndrome together with elevated levels of NT-proBNP are indicators of poor outcome (242).

Leyfman et al. discussed an interaction of IL-6 and hypoxia in COVID-19 patients. They postulated an interaction between viruses and different organs which led to IL-6 elevation (Figure 1 in (243)). In this depiction, hypoxia appears as an isolated element. This idea of disease can be found in many publications, e.g., (the graphical abstract in (112)), (Figure 1 in (244)).

COVID infection is related to glycolysis (245), therefore diagnostic imaging with 18F-FDG should demonstrate organs affected by hypoxia. The characterization of persisting symptoms of long-COVID has been recently demonstrated by Kiatkittikul et al., (246). The image panel shows a variety of 18F-FDG uptake patterns (Figure 10) including skeletal muscles, heart, vessels, and the lung. We interpret these changes as being related to hypoxia and consequently highly suggestive of CoQ10 deficiency and altered mitochondrial function.
A recent case report on hypoxia in COVID-19 infection was delivered by Serbanescu-Kele et al., in 2022 (247). The publication presented the decreasing course of oxygen saturation during hospital treatment. Quite unfortunately the authors utilized the term “happy hypoxaemia” ignoring the fatal outcome for the patient. Figure 1B of this publication showed the macroscopic appearance of a dark arterial blood sample which to our clinical understanding did not look happy at all (247).

The term happy hypoxia in relation to COVID-19 disease was used by Jennifer Couzin-Frankel in 2020 referring to the clinical experiences of Reuben Jesse Strayer, an emergency physician working at the Maimonides Medical Center, New York (248). It is quite important to know that the Jennifer Couzin-Frankel has a major in history of science, but no medical education and works as a staff writer for Science. Her article was not peer-reviewed and contained no scientific references. The original publication by Strayer on hypoxia and COVID-19 patients (249) was not cited. The original authors acknowledged that by 2020 little was known about the pathophysiology of COVID-19 disease. It is our personal feeling that this misleading and erroneous term should be banned from the literature.

A recent study of the UK Biobank, published 19 January 2023, found that cardiovascular disease and mortality were associated with long term COVID-19 disease. The authors could not identify conclusively any...
mechanism involved and simply provided a rather general and disappointing recommendation for ongoing clinical monitoring (250). Affected patients need indeed monitoring, however treatment implementation should be added since it has a higher ethical priority.

In 2022 Hansen et al., published an industry-backed study (Pharma Nord) that evaluated a high dose therapy with CoQ<sub>10</sub> in patients presenting a post COVID condition. A sound and scientific rationale for choosing the dose of 500mg CoQ<sub>10</sub> was not given (251). Initial and final CoQ<sub>10</sub> levels in the patients were not evaluated. The duration of CoQ<sub>10</sub> administration was quite short (6 weeks). In our experience, the combined supplementation with magnesium, selenium, and CoQ<sub>10</sub> starts to show recovery results after 9-12 months. Full recovery of the thyroid requires two to three years. Our recommended dose for CoQ<sub>10</sub> supplementation is 0.9mg/kg, i.e., app. 60mg/d.

1) Heat stress and cardiac disease – a pathogenesis proposal

Recently two publications have looked at the relationship between cardiac disease and heat stress. Ranek et al., described changes of heat shock proteins in heart failure, pointing towards the increased expression of hsp70, hsp90 and BAG-3 (252). In 2012 Iguchi et al., looked at cardiovascular and hormonal changes following heat stress produced by sitting in a heat stress chamber for 30 minutes at 73°C (253). They demonstrated that this stimulus had an elevation of hsp72 and prolactin. The increase in prolactin levels seemed related to the endurance capacity in response to exercise under heat conditions (254). Heat exposure and muscular activity can also affect blood magnesium levels inducing a severe decrease to sub-optimal levels (255).

Given these concepts, we can state that Ritossa observed the effects of an external heat source which led to the heat shock and the unfolded protein reactions. A modern view of heat shock response includes more toxic elements besides heat exposure. Trautinger provided the following description: “All organisms respond to sudden environmental changes with the increased transcription of genes belonging to the family of heat shock proteins (hsp). Hsp-inducing stress factors include elevated temperatures, alcohol, heavy metals, oxidants, and agents leading to protein denaturation. The induction of heat shock proteins is followed by a transient state of increased resistance to further stress, and the heat shock response is generally thought to represent an evolutionary conserved adaptive mechanism to cope with hostile environmental conditions” (256). Current knowledge of the complex processes involved in the hsp response describes essential interactions with ATP in the case of ATP-dependent hsp chaperones (257, 258). Alteration in protein structure will also involve the repair mechanisms of the unfolded protein response (259).

Heat stress has been investigated under clinical conditions. Bouchama, from Saudia Arabia, has published a series of studies dealing with heatstroke in humans. In 1995 a historical review on heatstroke included a discussion on the potential role of endotoxins in the disease (260). Recently the effects of acute, supra-physiological temperature stress have been examined at the transcriptome level. The test subjects were exposed to a mean temperature of 75°C in a sauna. The analysis of blood mononuclear gene expression revealed several patterns of change (Figure 2 in (261)). One key finding referred to altered mitochondrial function involving several complexes of the OXPHOS chain, including Complex I. Both electron transfer, as well as ATP production, were repressed. Bouchama et al., also identified an alteration of cytochrome C oxidase, corresponding to Complex IV (262). Both Complex I and Complex IV depend on iron-sulfur clusters for their function. Situations of physical exertion in hot environments with temperatures up to 41.5°C can be found in sports activities (263). Elevated temperature as a source of stress is not only limited to sports. It can also affect everyday activities (264). Furthermore, these changes are like those seen in heart failure, where the function of the OXPHOS chain is altered due to changes in Complex I and V (265). As a whole, ATP production can be disturbed (266). It must be kept in mind that the heat stress response requires sufficient ATP since some hsp are ATP-dependent (258). Experimental repeated exposure to heat stress can negatively affect the heat shock response of the heart (267). The increase of hsp70 levels after heat stress appears to decline with time, thus increasing the susceptibility of the heart to damage (268). This propensity to a myocardial injury can be corrected by CoQ<sub>10</sub>, resulting in higher hsp70 levels (128). In a similar study, the use of the selenium analog ebselen, resulted in improved expression of hsp70, which was associated with reduced myocardial infarct size (269).

Experimental work by Liedtke and Hughes in 1976 showed the detrimental effect of hyperthermia on cardiac specimens producing functional impairment together with increased glycolysis and lower ATP levels. The authors described the results as an additional energy drain to the heart (270). In 1989 Huang and Liedtke described the metabolic situation in re-perfused myocardium as being unable to synthesize ATP due to an inefficient electron transport and OXPHOS (271).

In a recent epidemiological analysis, Wang et al. described an association between previous heat stress situations and heart and kidney disease (272). Mechanisms leading to these changes were not discussed; however, these observations imply that heat exposure had left an altered biochemical system behind. Nzvere et al., have reached similar conclusions in
From the Thyroid to the Heart

We have briefly reviewed the role of diagnostic imaging keeping our eyes on glycolysis as demonstrated by 18F-FDG scans, and on fatty acid uptake based on the use of iodine-labeled methyl iodophenyl-pentadecanoic acid (BMIPP) (28). The clinical rationale for imaging these metabolic paths has been summarized by Yoshinaga et al. in 2007 (290). Contrasting with this structured description we must refer to a study by Dilsizian et al. where ideas about the interpretation of BMIPP scans were given. The conclusions offered by the authors had no profound biochemical foundation (291). What is useful in this publication is Figure 2 where a comparison between a heart perfusion and heart BMIPP study is shown. This image clearly shows that perfusion does not reveal metabolic changes (Figure 11).

II. Discussion and Outlook

Our clinically oriented literature review has disclosed that benign thyroid disease and several other entities including notable heart disease and COVID-19 share common features such as the symptom fatigue, and the events of hypoxia and glycolysis, elevated IL-6 levels, and the low T3 syndrome. We propose that CoQ10 deficiency plays a fundamental role in these diseases affecting the functionality of Complex I of the mitochondrial respiratory chain. The following Table contains an approximation to this process.

1. Initiation of glycolysis resulting from stabilization of HIF-1α (4). Interactions with CoQ10 and iron.
2. Increased production of reactive oxygen species follows functional alteration of respiratory Complex I (286)
3. Altered OXPHOS lead to reduced ATP production (287)
4. In situations of lack of oxygen – hypoxia - Complex I can be modified to a deactive state (288)
5. Experimental function loss of Complex I goes along glycolysis and with 18F-FDG uptake (289)

evaluating the long-term consequences of heatstroke on cardiac disease (273).

Heat stress is also a serious condition in human medicine (274). Heat stress per se stimulates the production of mitochondrial superoxide (275). The administration of dietary CoQ10 can attenuate oxidative changes produced by heat shock in chickens (276). A similar protection can be observed through administration of 300mg CoQ10 prior to heat exposure in elite swimmers (277). The production of mitochondrial small heat-shock protein (lmw Hsp) protects electron transport from CI to CIV (278). The authors declared that ubiquinone is the most thermo-labile protein in Complex I.

We have included this description keeping in mind the condition of postpartum cardiomyopathy (279) as studied by Cénac 30 years ago where the central deficiency was low selenium (280). Due to birth customs in Nigeria these women are exposed to extreme heat stress in the postpartum period. Experimental data on heat stress effects on the chicken heart has shown that these deleterious effects can be modulated by CoQ10 (281). An indirect hint on prolonged cardiac dysfunction following heatstroke was published by Zahger, Moses and Weiss in 1989 (282). A description of the characteristics of heat stroke and cardiac dysfunction published by Marchand and Gin were centered on thermoregulation and heat dissipation (Figure 1 in (283)). Other authors have found a relation between biomarkers and mortality after exertional heat stress where fatal cases had higher levels of NT-proBNP (284). A current view on heatstroke which does not consider the role of CoQ10 was published by Bouchama (285).
Metabolic imaging has been used to detect the footprint left by previous ischaemic episodes evident due to delayed recovery of myocardial metabolism (persistent dominant glucose utilization with suppression of fatty acid oxidation).

The following graphical allegory describes the medical setting relating hypoxia and cardiac disease. Superficial research has not considered biochemical changes sufficiently. Adding the biochemical background one can see that there are many more components to be explored. It is evident that keeping an eye only on the flow or on the uptake of $^{18}$F-FDG will not open a perception for fatty acid uptake. The following graphical allegory about the swimmer and the diver illustrates this situation (Figure 12).
Superficial view of the situation as seen by a skin diver, i.e., looking only at myocardial perfusion studies.

Deep view of the situation as seen by a scuba diver. A profound look will find hypoxia activation after CoQ₁₀ deficiency and hypoxia-related changes such as elevated IL-6, low T3 syndrome.

Figure 12: A. Graphical allegory - Myocardial perfusion studies correspond to the left image of the superficial snorkeling diver who sees nothing but flow. B. The lower panel shows the option to go deeper into the process by using additional gear signalized by the self-contained underwater breathing apparatus (SCUBA). This second image represents biochemical elements as described throughout the text. The images were taken from WikiCommons.

Additional data on the information delivered by BMIPP as compared to FDG can be found in publications authored by Yoshinaga (294). Yamagishi et al., summarized the impact of BMIPP and FDG diagnostic imaging going well beyond perfusion (Table 29 in (295)).

Looking beyond organ-related disease, the transmission of intergenerational trauma is a process that is also related to hypoxia and mitochondrial dysfunction (296).

Figure 13 illustrates our proposal on the essential biochemistry of resilience that maintains health.
Figure 13: The 2022 WOMED concept of resilience and health based on essential biochemical parameters.
Figure 14 illustrates our model of cardiac disease based on the information reviewed here. The model can be applied to other clinical conditions related to hypoxia.

**Figure 14:** The 2021 WOMED model of cardiac disease

### Literature


27. Chopra A. [123i]-B-Methyl Iodophenyl-Pentadecanoic Acid. Molecular Imaging and Contrast Agent


Supplemental information

A simplified clinical description of the symptoms of hypoxia has been published by the Cleveland Clinic.

Hypoxia: Causes, Symptoms, Tests, Diagnosis & Treatment (clevelandclinic.org)

An overview of causes and diseases related to hypoxia authored by Rhiannon Brett can be found in the Calgary Guide to Understanding Disease.

Hypoxemia: Pathogenesis and clinical findings | Calgary Guide (ucalgary.ca)