Ubiquinol as adjunctive therapy of heart failure

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Today in industrialized countries cardiovascular diseases are the leading cause of death. In the U.S., a significant increase in the incidence of congestive heart failure (CHF) has been found in the recent years. Researchers at the Henry Ford “Heart and Vascular Institute” in Detroit observed that the annual number of heart failure cases has more than doubled in the period from 1989 to 2012. Although a variety of drugs for the therapy of cardiac disorders is available, there is still a high risk to find the optimal treatment. Nutrients that are needed by the heart have the advantage that they are very safe and can safely be given at all stages of heart disease. Therefore, the adjunctive nutrient therapy represents a good and safe way to optimize the therapy of heart patients. Nutrients are not intended to replace the traditional medicines and therapies but rather supplement it. A nutrient concomitant therapy may lead to a reduction of the dosage of classical drugs or, at best, it even can be omitted entirely sometimes. The use of nutrients in the context of an adjunctive therapy in heart disease should always be done in consultation with and under the supervision of the attending physician.

Figure 1: Structures of vitamin E and K compared to Coenzyme Q10 and Ubiquinol

Energy deficiency in the myocardium is probably a dominant factor in heart failure and the attention is now increasing to look for substances and nutrients that stabilize the myocardial metabolism and that can maintain adequate energy production in the heart. A reduced myocardial content of essential metabolic components and natural antioxidants such as L-Carnitine, CoQ10, and Ubiquinol is found in patients with heart failure and the severity of the deficiency of these nutrients in the heart correlates with the severity of the heart failure. The more severe the heart failure has progressed the greater is the lack of the heart-active nutrients L-Carnitine and Q10 in the myocardium. Heart active nutrients such as L-Carnitine, CoQ10 and Ubiquinol meet all the criteria for a safe and adjunctive therapy in patients with symptomatic heart failure. They are free from side effects and improve the disease symptoms and the quality of life of patients by addressing one of the main causes of the lack of energy in the heart. Until today, several double-blind, placebo-controlled studies have been conducted with coenzyme Q10 supplementation in more than 1,000 patients and resulting in positive and statistically significant results in terms of various clinical parameters such as improvement in NYHA class, increased efficiency and decreased incidence of hospitalizations.

About Q10 and Ubiquinol

Coenzyme Q10 is a fat-soluble, vitamin-like nutrient, its chemical quinone structure is related with vitamin E and vitamin K (Fig. 1). Industrial Q10 and Ubiquinol are produced today via a patented natural process by yeast fermentation, which provides 100% nature-identical all-trans Q10.

Coenzyme Q10 and Ubiquinol with mitochondria act in all cells of the body within the mitochondria membrane but also in other cell membranes. In the mitochondria, Q10 and Ubiquinol interact with at least three mitochondrial enzyme complexes of the the oxidative phosphorylation and thus is directly involved in the ATP production [1].

This effect is particularly useful for clinical applications of Q10, and in specifically useful for cells with very high energy needs, such as heart muscle cells. The highest concentration of Coenzyme Q10 in the body is found in the heart. Coenzyme Q10 is located on the surface of the inner mitochondrial membrane. The Q10 content of the cells and organs is determined by the number of mitochondria and further determined by the concentration of Q10 within the mitochondria.

The saturation level of Q10 in the mitochondria is normally not achieved, so that the concentration of Q10 still can be increased in the mitochondria. Already a variation of plus or minus 25% of the Q10 content in the mitochondria, strongly influences the respiration rate of the mitochondria (Fig.2). Q10 is directly involved in 96% of the overall total cellular ATP production in the human body and thus particularly important for heart muscle function. Another fundamental characteristic of coenzyme Q10 is its antioxidant mode of action [2], which also is important for the mitochondrial membrane because Q10 protects the membrane against attacks from harmful free radicals from inside the mitochondria or from the cytosol, outside the mitochondria. Q10 protects particularly effective against hydroxyl radicals.

Coenzyme Q10 for the old heart?

Q10 is naturally present in all human tissues and is also synthesized by our body. Healthy young people can maintain healthy Q10 plasma levels by the synthesis of coenzyme Q10 and via the the absorption of Q10 from the daily diet. From the age of 40 years, however, the Q10 content decreases in all body tissues [3, 4]. The decline of the Q10 content in the heart is the most dramatic. Between the fortieth and eightieth year the heart loses up to 60% of its Ubiquinol/Q10 content (Fig. 3).

This decrease in the concentration in the heart of Q10 also leads to a reduction of the ATP-production in the heart and to a weakening of the heart. Why the heart loses so much Q10 loses with age, could be related to the loss of mitochondria of the heart cells with age. Mitochondria are extremely reactive cell areas because they process many nutrients during energy production including many oxygen reactions that can lead to the formation of reactive oxygen radicals, which can attack the mitochondrial membranes and ultimately destroy the mitochondria themselves. The loss of mitochondria then leads to a reduction of the concentration of Q10 in the heart and to a decrease in ATP-(energy)-production.

***Figure 2**: Increase in the mitochondrial respiratory rate due to an increased coenzyme Q10 content in the mitochondria*

Q10-/Ubiquinol deficiency as a risk factor for heart failure?

Coenzyme Q10 and Ubiquinol (also called QH) are natural nutrients that play an essential role in the energy system of the body, namely, in the ATP production in the mitochondria. Heart cells contain around 1600-2000 mitochondria per cell and they are dependent on an adequate supply of Q10 and Ubiquinol to ensure energy production. A lack of Q10 in the heart and in the heart cells leads to a reduced ATP production there and thus to a decline in cardiac function, whereby the whole body is affected. This raises the question whether a Q10 deficiency in the heart cells could be a risk factor for the development of cardiovascular disease. In fact, it has been shown that people with a congestive heart failure have a Q10 deficiency in the blood and heart muscle [5].

***Figure 3**: Falling Ubiquinol levels in human organs with increasing age*

The severity of heart failure correlates directly with the severity of the Coenzyme Q10 deficiency [6]. That means the more the heart failure progresses, the weaker the heart gets, the less Q10 and Ubiquinol are found in the heart cells. The same is also true for the L-Carnitine. It is unclear whether this lack of Q10/Ubiquinol and L-Carnitine is a cause or consequence of heart failure in the heart.

In healthy individuals, the plasma levels of coenzyme Q10 is about 1.0 ± 0.2 mg/l of blood. Certain diseases reduce the plasma levels of coenzyme Q10 to about 0.6 ± 0.2 mg/l and in people with severe heart failure often even lower values of 0.4 ± 0.2 mg/l can be found [7,8] which may indicate a serious deficiency of Q10 in the tissues.

Supplementation with coenzyme Q10 and Ubiquinol represents a treatment option as adjunctive therapy for the treatment of heart failure in all phases and at all levels of severity of the disease.

Effects of Q10/Ubiquinol on the heart

Coenzyme Q10 (CoQ10) and Ubiquinol can support heart health in congestive heart failure in various ways. First of all, it has a short-term, direct effect on the energy production in the heart:

In patients with heart failure it was found that a supplementation with CoQ10 increased the CoQ10 content in the heart and in the mitochondria of cardiomyocytes and also increased energy production in the heart and the ATP content in the heart [9].

Particularly in severely ill NYHA III and NYHA IV patients this leads often rapidly to a noticeable performance improvement, reduction of breathlessness etc. In this case the most critically ill seem to have the most noticeable benefit from an Ubiquinol and CoQ10 therapy, although the disease is already well advanced and the number of mitochondria has already fallen irretrievably in the heart cells of NYHA III and NYHA IV patients.

It would be desirable, therefore, as early as possible in the treatment of heart failure to begin. That is already in NYHA I and II patients, even if the patient is still relatively feeling well and few complaints are present, and therefore no large effects of Ubiquinol/CoQ10 therapy are noticeable. The aim of the Ubiquinol/CoQ10 administration in this case is to slow the loss of mitochondria in the heart cells, and thus the progression of heart failure.

Another approach would even be a preventive use of cardio active nutrients such as Ubiquinol/CoQ10, L-Carnitine and omega-3 fatty acids, for example, recommended krill oil at normal age-related heart for all people over the age of 50 years. For long-term administration of CoQ10 and Ubiquinol have direct and indirect effects on many cardiovascular risk factors:

- Increase in the CoQ 10 and ubiquinol content in the cardiac cells [Rosenfeldt 2005]
- Increase in ATP production in the heart cells [Rosenfeldt 2005]
- Increase in cardiac output and ejection fraction [Langsjoen 2009]
- Increase in the CoQ 10 content in LDL cholesterol [Mohr 1992]
- Reduction of LDL oxidation [Mohr 1992]
- Reduction of cholesterol synthesis [Schmelzer 2011]
- A positive influence on the vessel walls [Gao 2011]
- Reduction in blood pressure [Rosenfeldt 2007, Langsjoen 2009]
- Anti-inflammatory effects [Schmelzer 2011]

An increased CoQ10 concentration in heart cells and mitochondria has two main effects on cardiac metabolism: first, the ATP production increases when the CoQ10 content increases in the mitochondria and thereby the enzyme complexes I and II in the respiratory chain is activated and can be optimized. On the other hand causes a higher CoQ10 content in the inner mitochondrial membrane improved protection against oxidation, such as reactive oxygen species. This effect could then slow down the loss of mitochondria in the heart cells of CHF patients and thus slow down the progression of the disease itself.

This gives a rational why CoQ10 supplementation at the beginning of heart failure should be more effective because more mitochondria are present in which CoQ10 and Ubiquinol can be used to produce energy. In the early stages of the disease, cardiac cells still have many mitochondria.

However, their number decreases with progressive congestive heart failure. In the later stages of the disease, a CoQ10 supplementation can only interact with less mitochondria and can help their to optimize the metabolism in these remaining mitochondria.

Therefore Ubiquinol and CoQ10 have two important tasks in all cells:

- Increasing energy (ATP) production
- Protection of the mitochondrial membrane against oxidation

Clinical trials

Since the early 1990s, some studies have shown no beneficial effects of CoQ10 in heart failure. Criticisms of the design of these studies are low doses of CoQ10 and ubiquinol, too short CoQ10 supplementation and study period and thus starting the CoQ10 administration in too far advanced stages of heart failure. An optimum dosage of CoQ10 and ubiquinol in the treatment of heart failure had not been found yet in these studies. Already in 1967 K. Folkers and F. Enzmann supplemented children with muscular dystrophy Duchenne with 10 mg/kg Q10. The Q10 dosage used in clinical trials started with doses of 100 mg of CoQ10, which corresponded to three times the CoQ10 amount (30 mg) that was permitted at that time for supplements in Europe.

Today we know that a daily amount of 100 mg per day of CoQ10 is suboptimal for the majority of patients. This has researchers such as Peter Langsjoen (USA) prompted to use higher doses of CoQ10 over a longer period and to start as early as possible with the CoQ10 supplementation therapy, what the cardiac function in heart failure patients improved efficiency dramatically in many clinical observations.

The aim is to use higher dosages for a longer period of time to achieve higher plasma CoQ10 levels of greater than 2.5 mg/l or even more than 3.5 mg/l. In many cases this requires the supplementation of 600 to 900 mg CoQ10 or more per day. Better absorbable CoQ10 preparations should be preferred to achieve higher CoQ10 plasma levels with lower dosages.

In this context, a meta-analysis of 34 controlled trials and several open labelled and long-term studies were reviewed [13]. 23 out of 28 randomized, placebo-controlled trials with CoQ10 administration in congestive heart failure from 1972 to 2009 showed significant benefits of CoQ10 supplementation while only three studies showed no advantage. In these three studies, the plasma CoQ10 levels, however, were not increased above 2.5 mg/l, which would explain the results of creating no benefits due to a too low CoQ10 plasma level. One study in 49 patients who had been

resuscitated after cardiac arrest showed that supplementation with highly bioavailable nanofied CoQ10 significantly increased the survival rate (68% vs. 29%) [14].

In another study, 109 patients diagnosed with essential hypertension and congestive heart failure, were supplemented with an average of 220 mg of CoQ10 per day, thus reaching a CoQ10 plasma level of 3.02 mg/l. The NYHA class (New York Heart Association classification) of the patients improved significantly from a mean value of 2.40 to 1.36 (P <0.001) [15]. 51% of patients could stop other the use of any other antihypertensive drugs after an average intake of CoQ10 for 4.4 months, and could stop using 1-3 antihypertensive drugs.

In NYHA I and II patients it is possible to achieve the required therapeutic plasma level of about 2.5 mg/l or higher by administration of 200-300 mg CoQ10, but this is not possible anymore in NYHA III and IV patients. Patients with severe chronic congestive heart insufficiency (NYHA classes III and IV) often need extremely high CoQ10 dosages of up to 900 mg CoQ10 per day to reach sufficiently high plasma CoQ10 levels and even these high dosages are often not sufficient in many patients [9].

These patients often have very low plasma CoQ10 levels of less than 2.5 mg/l even after CoQ10 supplementation and achieve only limited clinical improvements by with supplementation with the classical CoQ10f form. It is assumed that existing intestinal edema greatly impair the CoQ10 absorption in these critically ill patients.

NYHA III and IV patients also have particularly low levels of CoQ10 in the heart and suffer from a large decrease in the ejection fraction of the heart.

When treated with CoQ10 therefore much higher plasma levels of CoQ10 must be targeted to increase also the pressure for CoQ10 to diffuse into the tissue cells to increase the tissue CoQ10 content especially in the heart. In the majority of studies in the past tissue levels of lower than 2.5 mg/l were achieved. Today the target value for plasma CoQ10 is >3.5 mg/l. In some studies CoQ10 plasma values of 6-8 mg/l were achieved especially by Ubiquinol supplementation.

In order to obtain higher plasma levels, it is important to optimize the bioavailability of CoQ10 preparations, which is quite low in general.

Recently, in the CoQ10 segment, the reduced form of CoQ10, which is called ubiquinol became available as dietary supplement. Ubiquinol is a much stronger antioxidant than the classical CoQ10 and extremely sensitive to oxygen. Therefore, for long time it was not possible to stabilize ubiquinol in a way that it could be used for the production of nutritional supplements.

Figure 4: Change in plasma CoQ10/ubiquinol levels in humans by ingestion of CoQ10 versus Ubiquinol

A few years ago Japanese researchers have managed to stabilize ubiquinol, and make it available for dietary supplements. CoQ10 and Ubiquinol can be easily distinguished visually: Ubiquinol is a white powder whereas CoQ10 is orange. If ubiquinol is oxidized it changes its colour from white to orange.

Since ubiquinol is available, it is also used in clinical trials. The number of clinical studies with ubiquinol supplementation has risen steadily, but the total number of existing clinical studies is still much lower in comparison to studies with the classic CoQ10.

It seems to have been a fluke, when it was found out that ubiquinol is much more bioavailable than its previously known oxidized form, the classic CoQ10. Ubiquinol seems to have a 4-6 times higher bioavailability in healthy people compared to the absorption of the conventional oxidised CoQ10 form [16, 17].

With dosages of 300 mg Ubiquinol per day already very high plasma levels of 6-10 mg / l can be achieved for the first time which would be great for NYHA III and IV patients and very helpful for the potential treatment of severe chronic heart failure. The mechanism why ubiquinol is so much better bioavailable than the classical CoQ10 has not yet been confirmed (Fig. 4).

The American scientist Peter Langsjoen first recognized in 2008 the potential of ubiquinol for the treatment of NYHA III and IV patients. He chose seven NYHA III and NYHA IV patients with extremely low ejection fraction of the heart (EF) of around 10-35% (mean EF 22%) for a supplementation study.

These patients received the full classical drug medication, and additionally 150 to 600 mg (mean 450 mg) conventional CoQ10 daily, but the CoQ10 levels in the blood of these patients were still lower than 2.0 mg/l, and no increase in the pumping power of the heart by the suCoQ10 supplementation was found. These patients were then switched to a mean intake of 580 mg of Ubiquinol (450-900 mg). As a result, the CoQ10 plasma levels increased in all patients by 3 - to 5 - fold compared to normal CoQ10. In five of seven patients the pump volume rose sharply and the NYHA class improved by one, two or even three classes in each case [18].

In another follow-up study Langsjoen included 29 NYHA II and III patients and replaced CoQ10 by Ubiquinol. Although patients received in average 50 mg less Ubiquinol than CoQ10 previously used (334 mg Ubiquinol instead of 384 mg CoQ10), the mean CoQ10 plasma level was almost doubled in all patients (from 2.9 mg/l to 5.3 mg/l) and their NYHA class decreased from 2.5 to 1.6 [19].

As a result of this study since then all heart failure patients at the Clinic of Dr. Langsjoen receive Ubiquinol supplementation as standard therapy before other any other classic heart medications drugs are given. The strategy of Prof. Langsjoen is to use such heart nutrients first and to optimize the nutritional status of the heart, and then to see what improvements occur and whether any other traditional heart medications are still necessary.

Beginning the treatment of heart failure with this new approach using safe nutrients without side effects often leads to clinical improvements in patients so that they need less classical medications, and sometimes some of them could completely go without any medication. Thereby reducing the dosage of classical heart medications also reduces the risk and the rate of side effects and drug interactions. This approach of an accompanying nutrient therapy even in severe disease and in combination with drugs is quite common in the US but much less known and used in Europe. In Europe nutritional therapies are still in its infancy and it would be desirable if more experts and medical doctors would use this alternative and safe option as a chance to treat their patients, especially the chronically ill patients that still receive often too many drugs at the same time every day and for many years.

Reduction of mortality by CoQ10

Many double-blind controlled studies have shown previously that CoQ10 reduces symptoms, and improves performance and quality of life in patients with heart failure and this without causing any side effects. But until now there has been no study which examined the impact on the survival rate of

patients with heart disease. In 2013 at the annual meeting of the "Heart Failure Association of the European Society of Cardiology" (Heart Failure Congress 2013) which was held from 25th to 28th of May in Lisbon (Portugal), the 2-year results of the Q-Symbio study were now presented.

Figure 6: Replacement of CoQ10 Ubiquinol by showing improvements in cardiac output in patients with severe heart failure (NYHA IV patients).

The Q-Symbio study is a randomized, placebo controlled, double-blind, multicentre study [20], which examined the effect of CoQ10 in patients with severe heart failure. Here, 422 patients (New York Heart Association (NYHA) class III or IV) with severe heart failure were randomized to receive either 2 mg of coenzyme Q10 per kg body weight or a placebo until today, now for more than 2 years. The primary endpoint of the study was the time measured until the occurrence of the first heavy heart and circulatory adverse event (MACE) which necessitated an unplanned hospitalization due to a worsening of the heart failure. Furthermore, the occurrence of cardiovascular-death, urgent cardiac transplantation and mechanical circulatory support were documented. Participating centres were in Denmark, Sweden, Austria, Slovakia, Poland, Hungary, India, Malaysia and Australia.

The results showed that CoQ10 supplementation reduced the risk of cardiovascular complications (MACE) almost by 50%. In the CoQ10 group significantly fewer patients namely 29 (14%) met the primary endpoint, compared to 55 patients (25%) in the placebo group ($p = 0.003$).

CoQ10 supplementation also halved the overall risk of death: in the CoQ10 group, 18 patients died (9%) compared to 36 patients (17%) in the placebo group ($p = 0.01$).

CoQ10-treated patients had a significantly reduced cardiovascular mortality ($p = 0, 02$) and had less frequent hospital visits because of their heart failure ($p = 0.05$).

In addition, there were also fewer side effects discovered in the CoQ10 group as compared to the placebo group ($p = 0.073$).

This study provides the first evidence that CoQ10 may reduce the overall mortality in patients with severe heart failure crucial. With these results, CoQ10 is the first substance that effectively reduces heart failure mortality since the development of ACE inhibitors and beta-blockers since more than a decade and it should be added to the standard treatment of heart failure today, as this was stated by the lead author Professor Svend Aage Mortensen (Copenhagen, Denmark).

This high efficacy of CoQ10 in such a serious illness is more than a surprise because CoQ10 is a nutrient and not comparable with a classical drug. As nutrient CoQ10 is extremely safe and has no side effects and can therefore be used without risk in all kinds of patients with severe heart failure.

So CoQ10 has clear advantages for the patient, but also for the physician because CoQ10 is another additional and safe option to help his patients. Professor Mortensen says, "CoQ10 is the first new drug to improve the survival in chronic heart failure and it should be added to the standard therapy of chronic heart failure. Other drugs for heart failure therapy are blocking cellular processes rather than to improve them and this can cause side effects. Supplementation with CoQ10, this natural and safe substance corrects a CoQ10 deficiency in the body and stops the vicious circle of chronic heart failure, namely by reducing the lack of energy in the heart."

The Q- Symbio study was performed with the classic, oxidised form of CoQ10 and a relatively low dosage of only 2 mg/kg body weight was used. Using the more bioavailable Ubiquinols in a higher

dosage of for example 300 mg Ubiquinol per day perhaps could be even more effective, what, however, only could be proven by another clinical study. CoQ10 is naturally occurring in many foods, including red meat, plants and fish, but the amounts are not sufficient to have an impact on heart failure. CoQ10 is available freely as a dietary supplement but patients who are already undergoing treatment for an existing heart failure nevertheless should seek advice from their medical doctor before taking additional CoQ10. Patients with ischemic heart disease, that receive statins as cholesterol lowering drugs, also benefit from CoQ10 supplementation, because statins reduce the CoQ10 synthesis in the body and this can lead to decreased CoQ10 plasma and tissue levels.

Professor Mortensen: "We have so far though no controlled studies showing that statin therapy plus CoQ10 reduces mortality more than statins alone. But statins reduce CoQ10 in the blood and in the muscle and also CoQ10 reduces oxidation of LDL effectively. So I think even ischemic patients on statin therapy should take CoQ10 in addition to the statins. "

Safety of ubiquinol and CoQ10

Coenzyme Q10 and Ubiquinol are sold as a dietary supplements since many years and have been tested in many published studies and clinical trials and were found to be completely safe and without any known toxicity or interactions with other medicines. The highest dosages that have been used in human studies were around 1,200 mg per day in patients with Parkinson's disease [21] and up to 3,000 mg per day in patients with familial cerebellar ataxia: In both cases, no side effects have been reported [22]. At least 39 studies of CoQ10 in heart failure have been published in which 4,498 patients received CoQ10 or Ubiquinol, with a remarkably good tolerability. Rarely, mild nausea was reported as a side effect. The long-term safety of CoQ10 was documented by Langsjoen [23] in a 6-year-long supplementation study of 126 patients with heart failure.

Dosages

Since 2007, the reduced form of CoQ10, called ubiquinol is available as a dietary supplement. Because of the improved bioavailability of ubiquinol it can be used in lower doses than conventional CoQ10. Effective dosages of ubiquinol are in the range of 100 to 600 mg per day. The aim is to achieve a level in the blood plasma ubiquinol is greater than 3.5 mg/l. For heart failure patients with NYHA class I and II is achieved by doses of 100-300 mg Ubiquinol. Patients in NYHA classes III and IV should have the highest possible plasma ubiquinol levels, and some people can reach 6-8 mg/l CoQ10 in the plasma achieved by the administration of 300-600 mg of ubiquinol.

Summary

CoQ10 and its reduced form, ubiquinol are both safe nutrients. Both can be used in healthy people and as an accompanying adjunctive therapy in patients suffering from heart failure. At the onset of heart failure the classical CoQ10 can still have a positive effect on the cardiac output, but in later stages of the disease Ubiquinol has been shown to be more effective. A therapeutically effective, physiological increase in cardiac metabolism can be achieved when the CoQ10 plasma levels is higher than 3.5 mg/l. CoQ10 and Ubiquinol are nutrients, thus not considered a medicinal product and therefore cannot replace conventional cardiac therapy. However, as part of an accompanying nutrient therapy, they are a great way to assist and support the conventional cardiac therapy in a safe way.

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