

Chapter 2

Context of Cardiac Diseases

In addition to aging, lifestyle, and environmental conditions, numerous structural and functional changes can alter the cardiovascular function. Health management is aimed at preventing or, at least, attenuating evolution rate by targeting risk factors, that is, supporting healthy eating and exercise and avoiding smoking tobacco, as well as screening populations at risk.

Research is thus devoted to: (1) discover the genetic causes of congenital heart diseases; (2) find new functional indices and exploration techniques for early diagnosis; (3) prevent evolutive complications; and (4) improve therapy using new efficient drugs with limited side effects and optimized medical devices and surgical procedures, of diseases of the heart and vasculature as well as the lung and blood, including sleep disorders.

2.1 Frequency of Cardiac Diseases

Cardiovascular diseases are the leading causes of death in rich countries that provoke about 12 million deaths per year worldwide. They account for more than half of all deaths in Europe of people over 65 years old. They are responsible for 33 % of all deaths in France. In France, about 4 people in every 10,000 die prematurely from heart disease, about 13 in every 100,000 from ischemic cardiopathies, and about 7 in every 100,000 from stroke. The rate can be increased by a factor 6 or more in other European countries.¹

The largest contribution comes from coronary heart disease that can be, at least in some countries, responsible for approximately 1 in every 5 deaths in men and 1 in every 6 deaths in women.

Cardiac pathologies remain the number one cause of death from congenital malformations in infancy (45–50 % of postnatal deaths due to congenital anomalies).

¹ Sources: Cité de la Science in Paris and European Health Status publication of the European Commission.

The majority of congenital heart defects arise from abnormal development of the valvuloseptal compartment.

Heart failure results from leakage or narrowing of heart valves (i.e., valvular insufficiency and stenosis), cardiac contractility insufficiency, disturbed electrical activation of the myocardium by the nodal tissue, among other causes.

2.2 Modeling of Cardiac Diseases

Two major arterial pathologies encompass aneurysms and stenoses due to atherosclerosis, which have been targeted by physical and mathematical modeling.

The major objective of validated computational models is to describe evolving quantities of interest, display fields of mechanical variables, demonstrate the role of governing parameters, and to predict short- and long-term behavior.

Animal models are aimed at understanding physiological and pathological processes, exhibiting factors involved in complex biological processes at various length scales, via histological and immunohistochemical analyses and genetic approaches, and evaluating drug effects, hence, improving therapeutic strategies. For example, apolipoprotein-E (ApoE)[−] and low-density lipoprotein receptor (LDLR)[−] mice can develop atherosclerosis both with and without high-fat feeding, hence their selection as a representative model of human situation. However, lesions that develop over a period of weeks do not mimic accurately those that evolve over decades in humans, in particular fibrous plaques as well as lesions with calcification, ulceration, hemorrhage, and/or thrombosis. Whatever the animal species, some mediators can lack or intervene at a different concentration. Therefore, the process in a given species can vary in comparison with that in another species. For example, cholesteryl ester transferase exists at a much greater level in humans than in mice. Conversely, HDL concentration is higher in mice than humans. In any case, all models are a simplification of the reality.

2.3 Risk Factors

Genetic and environmental risk factors contribute to the variability in disease susceptibility for cardiovascular diseases. The occurrence of cardiovascular diseases also depends on the subjected pathophysiological ground and habits.

The two most important risk factors are smoking addiction and abnormal ratio of blood lipids (apolipoprotein-B/apolipoprotein-A1 ratio). In fact, major cardiovascular risk factors include diabetes, hypertension, obesity, and the familial context (family members with heart diseases), in addition to hypercholesterolemia and smoking. Minor cardiovascular risk factors are age, high-stress job, sedentary habits, lack of daily consumption of fruits and vegetables, and high resting cardiac frequency (~ 1.25 Hz [75 beats/min]).

Table 2.1 Age score.
(Framingham point score;
Source: National Institutes of
Health—National Heart,
Lung, and Blood Institute)

Age	Point	
	Men	Women
20–34	−9	−7
35–39	−4	−3
40–44	0	0
45–49	3	3
50–54	6	6
55–59	8	8
60–64	10	10
65–69	11	12
70–74	12	14
75–79	13	16

The Framingham risk scores for men and women (Tables 2.1–2.5) are aimed at estimating the 10-year cardiovascular risk of an individual, more precisely, development of coronary heart diseases within the next decade in particular from plasma concentrations of lipids (total cholesterol and HDL-cholesterol [mg/dl]), value of the systolic blood pressure, and smoking habit. In fact, the LDL score is a better index than HDL and triglyceride scores [111].

2.3.1 Lifestyle

Lifestyle plays a major role in the prevention of complications of numerous chronic diseases. Although epidemiology does not give proof for the existence of a cause-and-effect relation, but provides statistical links between an investigated disease and explored parameters.

2.3.1.1 Inactivity

Inactivity can diminish life expectancy because it influences aging and predisposes to aging-related diseases. In particular, a relation was found between leukocyte telomere length and physical activity.

Table 2.2 Smoking habit score. (Framingham point score; Source: National Institutes of Health—National Heart, Lung, and Blood Institute)

	Points									
	20–39	40–49	50–59	60–69	70–79	20–39	40–49	50–59	60–69	70–79
NS	0	0	0	0	0	0	0	0	0	0
S	8	5	3	1	1	9	7	4	2	1

NS nonsmoker, S smoker

Table 2.3 Systolic blood pressure (BP) score (Framingham point score; Source: National Institutes of Health—National Heart, Lung, and Blood Institute)

Systolic BP (mmHg)	Men		Women	
	Untreated	Treated	Untreated	Treated
< 120	0	0	0	0
120–129	0	1	1	3
130–139	1	2	2	4
140–159	1	2	3	5
≥ 160	2	3	4	6

Moreover, combined to overnutrition, sedentary life causes obesity. Normal values of the *body mass index*, the ratio between the weight (kg) and the square height (m), range between 18.5 and 25. A value between 25 and 30 means moderate overweight; greater than 30, obesity. Obesity associated with adipose tissue dysfunction, characterized by infiltration of inflammatory cells and aberrant production of adipokines, yields an increased risk for metabolic and cardiovascular disorders, especially insulin resistance.

Sedentary lifestyle is associated with impaired endothelial functions exhibited by elevated plasma levels of endothelial microparticles [112]. Months of bed rest increase markers of endothelial dysfunction, such as circulating endotheliocytes and endothelial microparticles, which are released from the membrane of activated, injured, or apoptotic endothelial cells (Vol. 8—Chap. 5. Adverse Wall Remodeling), as well as impaired endothelial vasodilatory capacity (reduced cutaneous acetylcholine-induced vasodilation) [112].

2.3.1.2 Diet

Diet recommendations aimed at optimizing lipid and lipoprotein profiles, blood pressure values, glycemia, and body weight, currently rely on the consumption of plant-based foods, vegetables and fruits, and beverages that contain essential nutrients, such as vitamins (e.g., vitamin-B, -C, and -E), potassium, and magnesium,

Table 2.4 Total cholesterol score. (Framingham point score; Source: National Institutes of Health—National Heart, Lung, and Blood Institute)

Age	Points									
	Men					Women				
	20–39	40–49	50–59	60–69	70–79	20–39	40–49	50–59	60–69	70–79
<160	0	0	0	0	0	0	0	0	0	0
160–199	4	3	2	1	0	4	3	2	1	1
200–239	7	5	3	1	0	8	6	4	2	1
240–279	9	6	4	2	1	11	8	5	3	2
≥280	11	8	5	3	1	13	10	7	4	2

Table 2.5 HDL score.

(Framingham point score;
Source: National Institutes of
Health—National Heart,
Lung, and Blood Institute)

HDL (mg/dl)	Points	
	Men	Women
≥ 60	− 1	− 1
50–59	0	0
40–49	1	1
< 40	2	2

and healthy phytochemicals, such as flavanols, a subset of flavonoids.² In addition, vegetables and fruits have a low lipid and high fiber content, as well as an adequate sodium/potassium ratio.

Long-chain polyunsaturated ω 3-fatty acids such as docosahexaenoic acid (DHA) that abound in oily fish (e.g., anchovy, herring, mackerel, and salmon) protect the immune, nervous, and cardiovascular systems. In vascular smooth myocytes, DHA (but not its ethyl ester derivative) directly, rapidly, potently, and reversibly activates large-conductance, voltage- and Ca^{2+} -activated K^{+} channels (BK or $\text{K}_{\text{Ca}1.1}$)³ that acts as a vasodilator, thereby lowering blood pressure [113]. The BK channel is activated by intracellular Ca^{2+} and depolarization. It keeps the membrane hyperpolarized (negative feedback on cellular excitability). This proteic complex operates as a high-affinity receptor for DHA without needing Ca^{2+} ions. Lipid DHA is released from the plasma membrane by G-protein-activated, Ca^{2+} -dependent phospholipase-A2. The concentration required to activate BK channel is about 20 times lower than that needed to stimulate GPR120 involved in anti-inflammatory action of DHA [113].

Ester-conjugated ω 3-fatty acids refer to esterification with ethanol (i.e., ethyl esters) or with glycerol as triglycerides. Various ω 3 and ω 6-fatty acids as well as their ethyl and glycerol ester derivatives have distinct effects on BK channels and blood pressure when acutely applied. In particular, ethyl ester of DHA fails to reduce blood pressure. Oral or parenteral administration of these products thus has different clinical impact. In addition, the physiological response of healthy individuals and patients to various types of fatty acids may differ appreciably.

Flavonoids Flavonoids share a common basic chemical structure. Important flavonoid subsets encompass:

² Flavonoids (Latin *flavus*: yellow [golden or reddish yellow]) constitute a set of plant ketone-containing metabolites that comprise: (1) flavones derived from 2-phenylchromen 2-phenyl (1,4)-benzopyrone; (2) isoflavonoids derived from 3-phenylchromen 3-phenyl (1,4)-benzopyrone; and (3) neoflavonoids derived from 4-phenylcoumarine 4-phenyl (1,2)-benzopyrone. Flavanoids, a.k.a. flavan-3-ols and catechins, are nonketone polyhydroxy polyphenol compounds that share with flavonoids a 2-phenyl (3,4)-dihydro 2H-chromen 3-ol skeleton. Flavonoids (flavanols and flavanols) may have antiallergic, anti-inflammatory, antioxidant, antimicrobial, and anticancer effects.

³ These channels are composed of the pore-forming Slo1 and an auxiliary subunit. DHA activates vascular Slo1-BK β 1 and neuronal Slo1-BK β 4 channels [114]. Stimulation by DHA has a much smaller effect on Slo1-BK β 2 and Slo1-BK γ 1 channels [114].

- *flavonols* (e.g., kaempferol, myrestin, and quercetin [in onions]);
- *flavanols* (e.g., catechin and epicatechin [in cocoa, red wine, green tea, and apples]);
- *flavones* (e.g., apigenin and luteolin [in peppers]);
- *isoflavones*;
- *flavanones* (e.g., eriodictyol, hesperetin, and naringenin [in oranges]); and
- *anthocyanidines* (e.g., cyanidin, delphinidin, malvedin, and pelargonidin [in blueberries]), which are defined by the chemical residues attached to the basic flavonoid structure.

Flavanols are monomers and procyanidins are oligomers of flavanols.

Major flavanol sources include green tea (up to 300 mg/infusion), red wine, cocoa (up to 920–1220 mg/100 g), fruits, such as grapes, pears, berries, and especially apples (up to 120 mg/200 g). However, the flavanol profile (e.g., ⁻catechin and ⁺catechin as well as ⁻epicatechin and ⁺epicatechin) can vary considerably according to the food type.

Most of the flavanols in foods exist as oligomers (procyanidins). Only monomers and dimers are absorbed and rapidly metabolized. In plasma, ⁻epicatechin (5–250 nmol) represents a minor part of total plasma flavanols (<3 μ mol; short half-life) [115]. Epicatechin metabolites include methylated, glucuronidated, and sulfated adducts. Monomeric flavanols are further processed in the liver.

Endothelium-dependent (nitric oxide-mediated) vasodilation is related to the intake of flavanols in healthy subjects with cardiovascular risk factors (smoking, diabetes mellitus, hypertension, and hypercholesterolemia) [116]. In addition to the recovery of endothelial function, flavanol-rich diets improve insulin sensitivity, decrease blood pressure, and reduce platelet aggregation [115].

Regular, moderate consumption of some red wine reduces the risk of coronary heart disease. Red wines are sources of low levels of resveratrol and larger quantities of procyanidins. Procyanidins constitute a subclass of flavonoids. These vasoactive polyphenols lower blood pressure [117]. However, consumption of red wine alone cannot explain the French paradox (low rate of cardiovascular mortality in France despite high saturated fat consumption).

Chocolates and apples contain the largest procyanidin content (164.7 and 147.1 mg, respectively) with respect to red wine and cranberry juice (22.0 and 31.9 mg, respectively) [118]. However, the procyanidin content varied greatly between apple species with the highest amounts in Red Delicious (average 207.7 mg/serving) and Granny Smith apple (average 183.3 mg/serving) and the lowest amounts in Golden Delicious (average 92.5 mg/serving) and McIntosh apple (average 105.0 mg/serving). Flavonoid-rich cocoas contain monomeric flavanols (epicatechin and catechin) and oligomeric procyanidins formed from monomeric units. Both monomers and oligomers support cardiovascular health.

Cocoa and, hence, dark chocolate contain various active compounds, such as flavanols, theobromine, and caffeine, among others. The cocoa content varies greatly between chocolates; the flavanol profile and content differ strongly between cocoas. An inverse relation between flavanol-rich chocolate consumption and cardiovascular

disease risk (myocardial infarction and stroke) was observed in a middle-aged (35–65 years) German population of both sexes, without complications of cardiovascular diseases at the time of enrollment [119]. In the group with the highest chocolate consumption (7.5 g/d), both systolic and diastolic blood pressure are 1 mmHg lower on average than that in the low-chocolate consumption group. The group with the highest chocolate intake is also the group with the lowest vegetable diet.

Sulfides Excess salt intake over many years can lead to hypertension. On the other hand, garlic consumption is correlated with the reduction of risk factors of cardiovascular diseases. Garlic is rich in organosulfur compounds.⁴ Garlic-derived organic polysulfides are converted by red blood capsules and vascular cells into hydrogen sulfide [120]. The gasomediator hydrogen sulfide decreases blood pressure, protects against ischemic reperfusion damage, and induces O₂-dependent vasodilation.

Cheese and Fungus Metabolites Molded cheese, especially blue cheeses such as Roquefort, may favor cardiovascular health due to the presence of metabolites produced by *Penicillium roqueforti* of the Trichocomaceae set and other fungi, such as andrastin-A to andrastin-D and roquefortine, which can prevent cholesterol synthesis and bacterial growth [121].

Mediterranean Diet and Nitrofatty Acids The Mediterranean diet is characterized by a high consumption of unsaturated fatty acids, especially from olive oil and fish rich in oleic and linoleic acids, with vegetables rich in nitrite and nitrate, resulting in endogenous formation of reactive nitrofatty acids.⁵ In particular, linoleic acid and nitrite are major constituents of the Mediterranean diet that elevates concentrations of thiol-reactive electrophilic nitrofatty acids. The acidic and low-oxygen environment in the stomach enables an efficient nitration of such unsaturated fatty acids by nitrite. Nitro-oleic acid (or 9- and 10-nitrooctadeca 9-enoic acid [NO₂OA]) and other free and esterified fatty acid nitroalkenes are formed at elevated levels when unsaturated fatty acids are ingested together with a source of nitrite [123].

⁴ Allicin, the main organosulfur compound, is produced from amino acid alliin by alliinase and rapidly decomposes mainly into diallyl sulfide, disulfide, and trisulfide, and ajoene. After consumption, these compounds are rapidly metabolized.

⁵ The free radical nitric oxide can be added to unsaturated and hydroperoxy fatty acids. Nitrated fatty acids result from the reaction of nitrogen dioxide with unsaturated fatty acids. The NO₂ radical can form, according to the local oxygen concentration, nitronitrite and nitroallyl derivatives as well as lipid hydroperoxide. Nitrated derivatives of unsaturated fatty acids are formed under oxidative and nitrative stresses. In biological tissues, nitrofatty acids are produced by nonenzymatic reactions not only with NO[•] and NO₂[•], but also with peroxynitrite (ONOO[−]). Nitrofatty acids lodge in membrane phospholipids. Nitrated derivatives of arachidonic, eicosapentaenoic, linoleic, linolenic, oleic, and palmitoleic acids and their nitrohydroxy derivatives (nitrohydroxy oleate, linoleate and linolenate) can be also detected in human plasma and urine. In plasma, nitrofatty acids are free, bound reversibly to thiol-containing proteins, and esterified (as cholesterol esters). In plasma, nitrofatty acids are stabilized by incorporation into lipoproteins. Nitrofatty acids modulate macrophage activation, prevent leukocyte and platelet activation, and promote vascular relaxation [122].

The endogenous lipid electrophile nitro-oleic acid and other fatty acid nitroalkenes signal via pleiotropic mechanisms, such as activation of peroxisome proliferator-activated receptor (PPAR) γ (nuclear receptor NR1c3), the stress sensor and NFE2L2 sequestrator Kelch-like erythroid cell-derived protein with CNC homology (EHC)-associated protein KEAP1,⁶ and nuclear factor erythroid-derived-like factor NFE2L2-regulated antioxidant response genes, and inhibition of proinflammatory gene expression regulated by NF κ B [123]. Nitrofatty acids also inhibit lipopolysaccharide-induced cytokine expression and induce HO1 expression via activation of NFE2L2-regulated gene expression. Therefore, electrophilic lipid derivatives can control gene transcription that overall engenders an anti-inflammatory response.

Nitroalkenes react with nucleophiles, such as cysteine and histidine in various target proteins. In particular, they target transient receptor potential (TRP) channels in the central and peripheral nervous system [124]. Nitroalkene fatty acid derivatives can activate TRP channels on capsaicin-sensitive afferent nerve terminals, leading to increased smooth myocyte contractility via release of neuropeptides (neurokinins) and activation of Cav1.2b channel. Nitro-oleic acid activates TRPA1 and TRPV1 channels in sensory neurons involved in neurogenic inflammation and pain induced by noxious chemicals or thermal stimuli, thereby provoking calcium influx, membrane depolarization, and firing. In addition, high concentrations of nitro-oleic acid suppress firing in dorsal root ganglion neurons, hence contributing to anti-inflammatory effects.

Nitrofatty acids that can be detected in healthy human urine are produced at heightened levels during metabolic stress and inflammatory conditions (from nmol to μ mol concentrations) [124].

Nitro-oleic acid is a member of the category of electrophilic nitroalkenyl fatty acids formed by reactions between unsaturated fatty acids, nitric oxide (NO)- and nitrite (NO_2^-)-derived nitrogen dioxide (NO_2), these reactions being favored by the prooxidative condition of inflammation. In addition, when pH is low enough (< 6) to protonate NO_2^- to nitrous acid (HNO_2), this condition also yields the nitrating species NO_2 . Therefore, nitrogen dioxide is both a product of oxidative inflammatory reactions involving nitric oxide and nitrite and acidic conditions in the presence of nitric oxide or nitrite. Similarly, nitroalkenes are produced by addition of the radical nitrogen dioxide ($\text{NO}_2^\bullet$) to one or more of the olefinic carbons of unsaturated fatty acids [123].

⁶ In unstressed conditions, NFE2L2 is permanently ubiquitinated by the Cul3-(KEAP1)₂ protein-ubiquitin ligase complex and rapidly degraded in proteasomes. The KEAP1 homodimer binds to a single NFE2L2 molecule. Upon exposure to electrophilic and oxidative stresses, KEAP1 is modified and its ubiquitin ligase activity declines, thereby stabilizing NFE2L2 to induce cytoprotective gene transcription.

Linkage of electron-withdrawing nitro group to alkenyl groups confers a potent and reversible electrophilic reactivity to fatty acids. Fatty acid nitroalkenes can modify proteins covalently, thereby associating metabolic and redox signaling with the posttranslational regulation of target proteins.

Lipidic electrophiles mediate antihypertensive signaling, as they connect to soluble epoxide hydrolase (sEH; at Cys521 proximal to its catalytic site), thereby precluding its activity, especially hydrolysis of its vasoactive substrates epoxyeicosatrienoic acids (EET) [123]. EETs are metabolites of arachidonic acid processed by cytochrome-P450 epoxygenase. They are hydrolyzed into corresponding dihydroxyepoxyeicosatrienoic acids (DHET) by sEH. Upon sEH inhibition, EETs accumulate and provoke vasodilation, hence lowering blood pressure. The EET/DHET ratio is elevated in plasma.

Vasodilation is unaffected by inhibition of soluble guanylate cyclase. Nitro-fatty acids not only relax vascular wall, but also attenuate platelet activation and inflammation via a cGMP-independent mechanism [123].

Ketone Bodies Ketone body and anaplerotic metabolisms have been introduced in Vol. 6, Chap. 3. Cardiovascular Physiology.

Ketone Bodies in Cardiovascular Diseases Defective ketone body synthesis and catabolism are pathogenic factors. Conversely, some diseases disturb ketone body metabolism. Hepatic ketogenesis is suppressed at later stages of hyperinsulinemic obesity [125]. Ketone bodies participate in the regulation of mitochondrial metabolism, energetics, and ROS production.

Impaired cardiac energetics cause cardiomyopathy. Conversely, cardiomyopathies are associated with changes in energetic metabolism. In dilated and hypertrophic cardiomyopathies, the contribution of ketone bodies to cardiac energetics is augmented [125]. Decayed myocardial ketone body oxidation causes pathological outcomes.

In addition, hepatic ketogenesis is reinforced and circulating ketone body concentration rises during the development of heart failure. Ketone body metabolism may contribute to myocardial adaptation to ischemia–reperfusion injury, at least in rodents [125].

Ketogenic Diet Ketogenic diet raises blood levels of cholesterol and free fatty acids [125]. Anaplerotic 5-carbon ketone bodies and their precursor odd-chain fatty acids are proposed for the treatment of long-chain fatty acid oxidation (LCFAO) disorders. Ingestion of odd-chain fatty acids promotes hepatic C5-ketogenesis; β -oxidation of odd-chain fatty acids yields propionylCoA, an anaplerotic substrate that, in the liver, can also be packaged into C5 ketone bodies [125]. In extrahepatic cells, C5 ketone bodies are oxidized by CoA transferase SCOT, hence regenerating propionylCoA.

Dietary Phosphate A deranged calcium–phosphate metabolism and elevated phosphate concentrations are correlated with reduced life expectancy and cardiovascular events because of endothelial dysfunction, vascular calcification, and myocardial

hypertrophy [126]. Phosphate intake (by ingestion) and phosphatemia are indices of cardiovascular risk, not only in chronic kidney disease, but also in individuals with intact renal function [127].

Sources of Dietary Phosphate Sources of dietary phosphate include: (1) phosphate additives, i.e., inorganic phosphate salts (i.e., sodium phosphate) that serve as preservatives, flavor enhancers, color stabilizers, sweeteners, antioxidants, and emulsifiers, and (2) natural phosphate (phosphoproteins, phospholipids, phosphate esters, and phytates from milk products, fish, meat, and vegetables, respectively), i.e., organic phosphates in unprocessed foods.

Intestinal absorption is regulated by calcitriol. Natural phosphates are not only slowly and incompletely hydrolyzed but also slowly and incompletely (30–60 %) absorbed in the digestive tract in the presence of adequate vitamin-D levels [126]. On the other hand, inorganic phosphate is absorbed in the gut in larger proportions (80–100 %).

Calcium–Phosphate Metabolism and its Regulation Average western diets provide a daily phosphate intake of 1000–1700 mg according to food composition. The major determinant of plasma phosphate concentration is renal phosphate excretion; phosphaturia balances oral intake and intestinal absorption. Calcium and phosphate are regulated by parathyroid hormone (PTH), active vitamin-D, or calcitriol ([1, 25](OH)₂D₃),⁷ and fibroblast growth factor FGF23.

The major fraction of total body calcium localizes in bones, only a small part of calcium circulates in plasma as free (ionized) calcium (50 %) and binds to proteins (mostly albumin) as well as citrate, sulfate, and phosphate.

A reduced plasma Ca²⁺ concentration rapidly provokes secretion of PTH that inhibits renal calcium excretion and stimulates renal hydroxylation of 25OH-vitamin-D to calcitriol. The latter triggers intestinal calcium absorption (Table 2.6). In addition, calcitriol and PTH cause bone resorption by osteoclasts. Conversely, hypercalcemia inhibits PTH secretion via parathyroid calcium-sensing receptors.

FGF23 The master regulator of renal phosphate handling is fibroblast growth factor FGF23 liberated by osteocytes upon high calcitriol and phosphate levels, rather than PTH. Factor FGF23 is mainly synthesized and secreted by osteoblasts stimulated by calcitriol, PTH, and hyperphosphatemia.

Target cells of FGF23 comprise renal and parathyroid gland cells as well as cardiomyocytes [126]. In the kidney and parathyroid glands, FGF23 interacts with β -glucuronidase Klotho coreceptor. Membrane-bound Klotho selectively localizes

⁷ Humans regularly exposed to sunlight synthesize adequate concentrations of vitamin-D. Solar ultraviolet-B waves convert 7-dehydrocholesterol to previtamin-D₃ (or precholecalciferol), which spontaneously isomerizes to vitamin-D₃ (cholecalciferol). Otherwise, few food components contain sufficient vitamin-D, such as fish liver, fatty fish, and egg yolks. Vitamin-D receptor lodges in myocardial and vascular cells. Calcitriol represses the renin–aldosterone axis, causes insulin secretion and sensitivity, prevents proliferation of vascular smooth myocytes and hypertrophy of cardiomyocytes, and can exert immunoregulatory functions.

Diseases of the Cardiac Pump

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