

## Biomarkers of corticosteroid-induced hypertrophic cardiomyopathy in preterm babies

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## 1. ABSTRACT

The study of biomarkers and their signaling pathways has led to the development of new therapeutic strategies in a number of disorders. The purpose of the present systematic review is to provide an overview of different biomarkers in preterm newborns with corticosteroid-induced hypertrophic cardiomyopathy (CCHC). Several pathophysiological biomarkers are presented and discussed with the aim of investigating their diagnostic and prognostic value, particularly in relation to the potential progression of the disease and/or mortality in adulthood. This investigative approach may not only provide pathophysiological information on this serious drug-induced adverse effect, but also suggest novel therapeutic approaches to be applied in controlling its harmful consequences.

## 2. INTRODUCTION

The development of cardiac hypertrophy in preterm infants induced by corticosteroids (CCs) administration has been well known for a long time. It includes an increase in the size and disarray of cardiomyocytes, a reduction in their number, and heart fibrosis. In this review, we summarize current knowledge of the mechanisms underlying the preterm's hypertrophic cardiomyopathy that occur with CCs administration. These include hormones, growth factors, apoptotic and myonecrosis markers, molecules involved in both endothelial and platelet functions, inflammatory cascade, wall stress markers, and profibrotic factors. At the end of the review a pathophysiological model linking the above stated biomarkers in CCHC is proposed. We also discuss how these biomarkers are useful in determining prognosis

of this drug adverse effect after its apparent remission. Finally, the study of these biomarkers and their signalling pathways might enhance the investigation of new therapeutic strategies with the aim of modifying the natural course of the disease.

### 3. CORTICOSTEROIDS IN NEONATAL INTENSIVE CARE UNIT

#### 3.1. Corticosteroids and chronic lung disease in preterm newborns

The use of postnatal CCs in the treatment and prevention of Chronic Lung Disease (CLD) in preterm newborns has been subject to considerable debate in the past. Particularly in the early 1990s, administration of CCs was applied extensively to prevent or reduce the incidence and severity of CLD in Neonatal Intensive Care Units (NICU), with Dexamethasone (DEX) being the most widely used drug (1). This extended use was justified mainly by the therapeutic effect of CCs in improving respiratory function, in reducing the need for both mechanical ventilation and oxygen administration, and in producing a decrease in mortality (2). However, in view of the numerous short- and long-term adverse effects induced by CCs, in 2002 both the American Academy of Pediatrics and the Canadian Paediatric Society advised against their postnatal use in the treatment or prevention of CLD in preterm infants, suggesting the drugs be administered solely in extremely serious clinical circumstances (preterm newborns with maximum ventilatory and oxygen administration support) (3). In spite of the above divergent opinions, CCs continue to be widely administered, particularly in suburban NICU. However, even units adopting more advanced therapeutic protocols continue to administer CCs to selected infant populations (i.e. those depending on mechanical ventilation and having a chest X-ray predictive for CLD on day seven) (4).

#### 3.2. CCs-induced hypertrophic cardiomyopathy

As stated above, concerns have been raised with regard to the wide range of CCs side effects. Short-term side effects reported to affect the cardiovascular system include myocardial hypertrophy, the so-called CCHC. It is well known that post-natal therapy with DEX for 2-3 weeks may determine a left ventricular walls thickening, with consequent possible obstruction of the left ventricular outflow tract, that generally regresses after withdrawal of treatment (5,6). In detail, the relative risk calculated for the development of CCHC is 4.39 (95% confidence interval: 1.40-13.37) in infants receiving early DEX treatment (less than 36 hours) and 14.3 (95% confidence interval: 1.20 - 67.69) in infants undergoing a moderately early DEX treatment (7-14 days) (7,8). Another study demonstrated a severe cardiomegaly at chest X-ray in preterm infants following CCs therapy. Accordingly, cardiomegaly may represent a valid radiographic marker to be considered in the clinical management of these patients (9). A similar cardiac adverse effect was also produced following use of methylprednisolone and hydrocortisone, two other CCs used against CLD in NICU (10,11). With regard to the pathophysiological mechanism of this drug-induced adverse effect, prolonged CCs therapy

in young infants and premature neonates is known to induce increased protein synthesis in myocytes, leading to hypertrophy. These changes are usually transient, resolving within 1-2 weeks of discontinuation of CCs (12,13). Many cases of CCHC have been encountered in clinical practice. At times only a transient thickening of ventricular walls has been reported, in the absence of left ventricular outflow tract obstruction. Following withdrawal of CCs, ventricular hypertrophy generally disappeared (14). Conversely, in other cases DEX induced both left ventricular outflow obstruction and congestive heart failure (5). These haemodynamic and clinical developments are likely to require medical intervention to relieve left ventricular outflow tract obstruction and the signs and symptoms of heart failure (15). A clinical case has been reported of a preterm infant suffering from CCHC and obstruction of the left ventricular outflow tract causing decreased coronary artery perfusion, and consequent transmural myocardial infarction (16). Due to the potential rapid, significant changes in ventricular wall thickness and outflow obstruction, the performing of frequent, repeated echocardiographic examinations is recommended (17). Recent studies have suggested that neonatal DEX treatment may have detrimental long-term effects on the heart, possibly initiated by inhibiting the cardiomyocyte mitosis, and resulting in a reduced number of cardiac muscle cells in adulthood (18). These changes appear to elicit a late systolic dysfunction, due to compensatory cardiac dilation (19). The damage may lead to a reduction in life expectancy as observed in rats treated with DEX in the neonatal period (20).

#### 3.3. Morphological and microscopic characteristics of CCHC

CCHC is macroscopically characterized by asymmetric thickening of the ventricular walls, and reduction in intracavity dimension (12,21). Microscopic characteristics observed in CCHC reveal a decreased number of cardiomyocytes, whereas cell length and cell volume are increased, indicating cellular hypertrophy, apparently compensating for the lower total number of cells. Fibrosis is a further important pathophysiological component of this acquired cardiomyopathy. A loss of balance between ventricular walls and small intramural vessels may also be detected (18,20-22). Histological examination confirms the cardiac effect produced by DEX, resulting in an increased collagen deposit between myocytes. Foci of myocytolysis are more frequently present in the subendocardium and midmyocardial cells than in subepicardial cells, and to a lesser extent surrounding the vessels. Macrophages are present around myocytolysis sites. Their increased number and the presence of lymphocytes underlines the onset of low grade inflammation. Mast cells are mainly present in the vicinity of blood vessels (21,23).

#### 3.4. Biomarkers associated with CCHC

Biomarkers are molecules suited to objective measurement by means of laboratory techniques, capable of providing useful information on adverse drug reactions, abnormal pathophysiology and prognosis, as well as in enhancing differential diagnosis.

**Table 1.** Biomarkers of hypertrophic cardiomyopathy induced by corticosteroids administration

Class	Biomarkers	Action
Hormones	catecholamines	Hypertrophy
	TGF-beta	Fibrosis
	Ang-II	hypertrophy/fibrosis
Growth factors	?	hypertrophy
Apoptotic biomarkers	?	myocytolysis
Troponins	cTnT	myocyte injury
Endothelial biomarkers	ET-1	endothelial damage
	ADMA	endothelial damage
	vWf	endothelial damage
Prothrombotic	PAF	biomarkers thrombotic status
	PDGF	thrombotic status
	fibrinopeptide A	thrombotic status
	TAT	thrombotic status
	F1+2	thrombotic status
Inflammatory biomarkers	TGF-beta	fibrosis
	IL-6	hypertrophy
Cardiac walls stress biomarkers	ANP	atrial walls stress
	BNP	ventricular walls stress
	NTpBNP	ventricular wall stress
Metalloproteinases	MMPs	fibrosis
	TIMPs	collagenolysis

Transforming growth factor-beta (TGF-beta), angiotensin II (Ang-II), troponin T (cTnT), endothelin (ET-1), asymmetric dimethylarginine (ADMA), Von Willebrand factor (vWf), platelet-activating factor (PAF), platelet-derived growth factor (PDGF), fibrinopeptide A, thrombin - antithrombin III complex (TAT), F1+2, tumour growth factor- beta (TGF- beta), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), atrial natriuretic peptide (ANP), B-type Natriuretic Peptide (BNP), N-terminal-Pro-BNP (NTpBNP), matrix metalloproteinases (MMPs), and tissue inhibitor of matrix metalloproteinases (TIMPs)

Whilst the administration of CCs to preterm infants in severe clinical conditions cannot at times be avoided, research is currently focusing on the identification of markers capable of predicting both the development and severity of their adverse effects, including the CCHC. A number of diverse mechanisms (such as hormonal action, apoptosis, myonecrosis, fibrosis, growth factor influence, endothelial dysfunction, coagulation and platelet activation, inflammation, cardiac wall stress and extracellular matrix degradation) are involved. Numerous molecules implicated in each of these pathophysiological pathways can be detected in the blood, providing information on subgroups of patients at potential increased risk for subsequent cardiovascular events. The purpose of this review is to identify appropriate biomarkers that may provide potential tools for use not only in the diagnosis and stratification of these patients, but also in understanding the typical clinical and pathological characteristics of this harmful iatrogenic complication (Table 1).

### 3.5. Search strategy

A comprehensive literature search was performed using electronic bibliographic databases (MEDLINE, EMBASE, The Cochrane Library, and DARE) and combinations of the following keywords: treatment, hypertrophy, cardiomyopathy, corticosteroids (CCs), dexamethasone (DEX), methylprednisone, hydrocortisone,

hormones, fibrosis, apoptosis, catecholamines, proto-oncogenes, c-fos, c-myc, c-jun, transforming growth factor-beta (TGF-beta), renin-angiotensin-aldosterone system (RAAS), angiotensin II (Ang-II), nuclear factor of activated T cells (NFAT), cortisol, s-Fas, s-FasL, tumour necrosis factor-alpha (TNF-alpha) and beta (TNF-beta), cardiac troponin T (cTnT), glucocorticoids, endothelin (ET-1), asymmetric dimethylarginine (ADMA), von Willebrand factor (vWf), platelets, platelet-activating factor (PAF), platelet-derived growth factor (PDGF), fibrinopeptide A, thrombin - antithrombin III complex (TAT), thrombotic, prothrombotic fragment 1 + 2 (F1+2), inflammation, transforming growth factor- beta (TGF- beta), cytokines, interleukin-6 (IL-6), atrial natriuretic peptide (ANP), B-type Natriuretic Peptide (BNP), N-terminal-Pro-BNP (NTpBNP), matrix metalloproteinases (MMPs), and tissue inhibitor of matrix metalloproteinases (TIMPs). Bibliographies of all selected articles and review articles were carefully reviewed for mention of other relevant articles. Where necessary, the authors were contacted to obtain further data.

### 3.6. Hormones

Several studies have shown the effect of CCs in increasing the circulating catecholamines (24-27). The role of humoral mechanisms, including catecholamines, in the regulation of CCHC in newborn has been extensively evaluated. This stimulation is dose-related, and not associated to a sustained chronotropic effect (28). The alpha- and beta-adrenergic stimulation of the rat heart produces cardiac hypertrophy, which is preceded by an early, more pronounced and longer lasting expression of the proto-oncogenes c-fos and c-myc (29). Both alpha- and beta- stimulation appear to produce growth-promoting effects on cultured isolated myocytes, presumably implicating different mechanisms. However, although catecholamines are implicated in this effect, their quantitative importance remains to be determined. It has been hypothesized that catecholamines may play a role in transition from the adaptive to the maladaptive state of cardiac hypertrophy (30). TGF-beta 1 is a major pro-fibrotic factor. Neonatal DEX induces a TGF-beta 1 over-expression, thus affecting the normal heart growth by increasing the collagen production in fibroblasts. TGF-beta 1 is assessable in blood (20,23,31,32). Likewise, a key role appears to be played also by the RAAS. Indeed, DEX exerts a direct stimulation on the angiotensin-converting-enzyme in neonatal rat myocytes, thus eliciting the production of Ang-II (33). *In vitro*, Ang-II induces not only mRNA expression of the proto-oncogenes c-fos, c-myc, and c-jun in cardiomyocytes and fibroblasts, but also hypertrophy and/or hyperplasia of these cells (34,35). A recognized mediator of Ang-II-induced cardiomyocyte growth is nuclear factor of activated T cells (NFAT). All these changes are reversed by the Ang-II inhibitor losartan (36,37).

### 3.7. Growth factors

A recent report has provided substantial convincing evidence that cortisol - the most important endogenous mineralocorticoid - acts as a growth hormone in ovine fetal heart, stimulating cardiac myocyte

hyperplasia (38). Perinatal administration of cortisol in fetal lambs was shown to stimulate the hypertrophic myocardial growth pattern (39). Consequently, in the adult heart it has been postulated that the onset of several adverse effects, such as cardiac hypertrophy and fibrosis, may be due to the occupancy and activation of mineralocorticoid receptors by endogenous CCs (40,41). On the basis of these observations, it could be hypothesized that synthetic CCs, by acting on mineralocorticoids' receptors of neonatal rat like agonists, may produce a diffuse myocardial hypertrophy. This mechanism however is merely putative and should be further investigated.

### 3.8. Apoptotic biomarkers

The acquired hypertrophic cardiomyopathy induced by CCs in preterms results in a reduced number of cardiomyocytes due to apoptosis. Accordingly, hypertrophy appears to act as a compensatory mechanism for the lower total number of cardiac cells (18,42). However, to date the actual biochemical mechanisms and molecular signalling (s-Fas, s-FasL, TNF-alpha, and TNF-beta) involved in this process remain to be clarified.

### 3.9. Myonecrosis markers: troponin

The mechanism of myocyte injury in CCHC is poorly understood. A possible role may be played by the relative ischemia induced by a lower capillary density (21,42). cTnT is a highly sensitive, and specific biomarker of myocardial injury. Indeed, postnatal DEX treatment led to an increase in cTnT, previously shown to be involved in the onset of cardiac hypertrophy and correlated with echocardiographic parameters of cardiac performance in preterm infants (43-45). Sato *et al.* demonstrated how cTnT levels correlated with thicker interventricular septum. In addition, some patients with hypertrophic cardiomyopathy and high levels of cTnT subsequently developed a dilated cardiomyopathy. To this regard, the measurement of cTnT may be helpful in determining the effects of CCS treatment on the evolution of hypertrophic cardiomyopathy, and in identifying patients at higher risk of developing a late heart failure (46). Further studies should however be undertaken on this issue.

### 3.10. Markers of endothelial function

Microvascular dysfunction is a common finding in adult patients affected by hypertrophic cardiomyopathy and its extent is an important prognostic marker (47). Similar findings are to be expected for acquired cardiomyopathy in preterm infants. Extravascular compressive forces seem to play an important role in the microvascular dysfunction implicated in hypertrophic cardiomyopathy (48). Because of the pressure overload, the ET-1 mRNA synthesis is upregulated in hypertrophied hearts. ET-1 vasoconstrictive effect is further emphasized by CCs-stimulated glycolysis (43, 49-51). Following DEX administration, both ET-1 and ADMA release increase significantly, thus performing a pivotal role in the initiation of stress-related endothelial dysfunction (52). Moreover it confirms that in early life elevated ADMA levels may announce a developmental programming of cardiovascular morbidity (53). In addition, an increase in plasma levels of vWF, an established marker of endothelial

damage/dysfunction, was reported as a result of high-dose DEX (54). However, two previously published articles reported no statistically significant differences in vWf levels between patients with HCM and healthy matched controls (55,56). In our opinion vWf levels are nonspecifically elevated in premature infants with CLD and are likely related to specific pulmonary endothelial injury (57).

### 3.11. Platelet function and prothrombotic markers

Postnatal administration of DEX increases the PAF and the total number of platelets, although it is not clear whether these cells play a role in the pathogenesis of CCHC (58,59). On the other hand, a pathological characteristic of hypertrophic cardiomyopathy is intimal and/or medial hyperplasia of intramyocardial small vessels. Since PDGF has the potential to induce proliferation of vascular smooth muscle cells, fibroblasts, and endothelial cells, platelets may be involved in the development of intramyocardial vasculopathy (60,61). Although to date no studies have been undertaken to investigate the production of PDGF in platelets of preterms affected by CCHC, the possibility of an increased production cannot be ruled out. Likewise, it cannot be excluded that PDGF production may originate from other cells, including hypertrophied myocytes (61). In the future, the inhibition of PDGF signalling by means of receptor antagonists could open a new field in the treatment and prevention of CCs-induced neonatal heart hypertrophy and related long-term adverse cardiac effects, although further studies are mandatory. CCs administration, particularly at high doses, is complicated by adverse outcomes, including thrombotic events. The same turbulent flow in an obstructive cardiac ventricle might be involved in the prothrombotic state through an increase of shear stress (54,62). Thromboembolic events in adults with hypertrophic cardiomyopathy are frequently observed. Studies conducted on a limited number of patients have reported significantly increased plasma levels of fibrinopeptide A, TAT, and F1+2, as markers of fibrin generation and reflecting thrombotic status, compared with normal subjects (62,63). A similar occurrence may likely be manifested in CCHC.

### 3.12. Inflammatory biomarkers

As stated in the section on Morphological and microscopic characteristics, a number of inflammatory cells (macrophages, lymphocytes, and mast cells), underlying low grade inflammation, are present in the hypertrophied cardiac muscle of preterm infants treated with CCs (23). Both macrophages and lymphocytes may be associated with increased fibrosis manifested through activation of inflammation mediators, such as TGF-beta (64,65). Moreover, mast cells, are capable of stimulating collagen expression from heart fibroblasts by releasing fibrogenic protease chymase-dependent TGF-beta, which in turn releases TGF-beta and activates Ang-II (31). Furthermore, both macrophages and mast cells, under different conditions, secrete a number of interleukins, including IL-6, and may contribute towards the onset of myocardial dysfunction by secreting TNF-alpha (64-67). It is possible

that an increase in mechanical overload may be the possible trigger factor that stimulates the production of both IL-6 and TNF-alpha (68). The overexpression of IL-6 and IL-6 receptor in mice leads to the development of cardiac hypertrophy (69). It is feasible to hypothesize that the same path may occur in humans. Indeed, TNF-alpha has been detected in several human cardiac-related conditions, including hypertrophic growth response in cardiac myocytes (70). Both IL-6 and TNF-alpha are expressed in the myocardium, during various conditions of stress, and are capable of modulating cardiac function, even by inducing ventricular hypertrophy and fibrosis (69, 71-74). It is plausible to maintain that TNF-alpha might be involved in the pathogenesis of CCHC in preterm newborns, although the mechanism underlying this process remains to be established. Elevated TNF-alpha levels may identify patients affected by a more severe cardiomyopathy, as well as the progression of an CCHC to a dilated cardiomyopathy in adulthood (72).

### 3.13. Wall stress markers: natriuretic peptide

The use of natriuretic peptides in the neonatal population is on a constant upward trend. ANP is synthesized predominantly in the atria in response to elevated wall stress. Postnatal DEX treatment leads to an increase in cardiac level of ANP mRNA, which seems to be linked to the development of cardiac hypertrophy and dysfunction (37,43). BNP, and NTpBNP are becoming increasingly recognized as a potential screening tool for patent ductus arteriosus, and as a marker of myocardial performance (75). Numerous kits are currently available for BNP measurement. This has led to discrepancies in cut off levels in studies performed to assess the prognostic and haemodynamic properties of BNP. On the other hand, the markedly more limited number of kits used in measuring NTpBNP makes this molecule more suitable for routine clinical monitoring and comparison between different studies (76). NTpBNP is an effective means of screening for hypertrophic cardiomyopathy in children, because in this population the sensitivity of electrocardiography and echocardiography alone is relatively low (77). In addition, NTpBNP is correlated with echocardiographic measures of cardiac performance in preterm infants (45). A study performed on newborns with hypertrophic cardiomyopathy induced by maternal diabetes, revealed significantly different NTpBNP levels compared to those recorded in offspring from healthy mothers (78). On the basis of this finding, a similar study should be focused on preterm infants with CCHC.

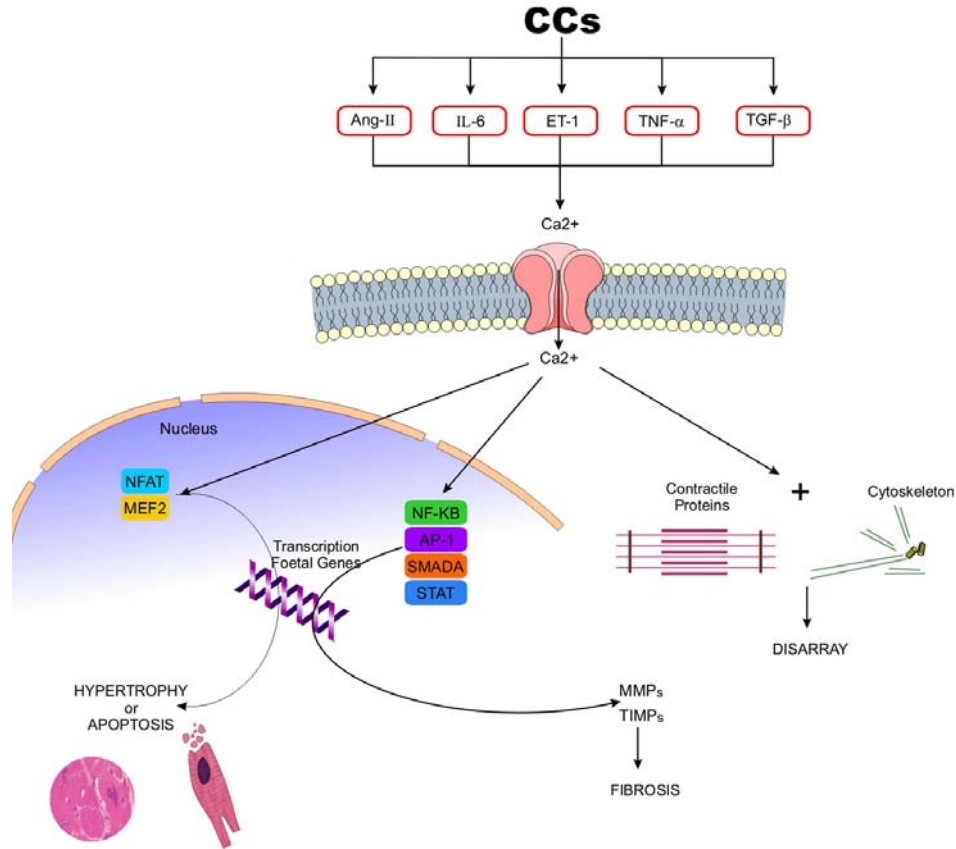
### 3.14. Matrix metalloproteinases

MMPs are zinc-dependent endopeptidases with collagenase activity. They are capable of degrading various extracellular matrix proteins, as well as to process a large number of bioactive molecules. MMPs play a pivotal role in cardiac remodelling and fibrosis in a number of cardiovascular diseases, including myocardial infarction and development of dilated cardiomyopathy. MMPs are inhibited by specific endogenous TIMPs, that comprises a family of four protease inhibitors (TIMP-1 through 4) (79). The expression of MMPs and TIMPs is influenced by numerous molecules, including some of those mentioned

above as biomarkers of CCHC: RAAS, oxidative stress markers, ET-1, TNF-alpha, and TGF-beta (80). The high degree of fibrosis characterizing the CCHC could be due to an imbalance between MMPs and TIMPs, with consequent accumulation of fibrous tissue. In hypertrophic cardiomyopathy, a reduction in MMP-1, and an increase in TIMP-1, TIMP -2, TIMP-4, MMP-2, and MMP-9 have been reported (81-83). These changes result in enhanced collagen turnover and development of fibrosis. In addition, MMP-2 correlates negatively with systolic function, which is reduced in late cardiac dilation phase of CCs-induced HCM, while a positive correlation has been shown between TIMP-2 and left ventricular dimensions (19,83). MMP-9 appears to be an independent factor associated with late Gadolinium enhancement in cardiac magnetic resonance imaging, an established non-invasive method to assess the presence of fibrosis (84). Furthermore, both MMP-2 and MMP-9 are involved in the pathogenesis of CLD itself, and their levels are not reduced by antenatal CCs therapy (85). It should be underlined that MMPs measurement has been proposed for use in the follow-up of patients affected by hypertrophic cardiomyopathy, with an aim to assessing the beneficial effects of different treatments (86). An increased deposition of collagen have been observed in infants with CCHC (21). Knowledge of the way in which upstream molecules regulate MMPs may provide useful clues to be applied in the development of innovative therapeutic interventions. In animal models, several drugs capable of inhibiting MMPs activation have displayed a potential to reverse or attenuate interstitial fibrosis. Specifically, treatment with losartan, spirinolactone, and N-acetylcysteine decreases the expression of collagen 1-alpha and TGF- beta in mutant mice, thus reducing interstitial fibrosis (86-88). To date, findings reported in literature have suggested the presence of a disturbed balance of collagen synthesis and degradation with a predominance of collagenolysis inhibition and collagen accumulation (fibrosis). MMPs are probably associated with mechanisms of remodelling in patients with CCHC, and progression to systolic dysfunction and heart failure, increase of left ventricular wall thickness and late cardiac dilation.

### 3.15. A proposed pathophysiological model linking biomarkers in corticosteroid-induced hypertrophic cardiomyopathy

A considerable number of the above stated stimuli, including Ang-II, TGF-beta, ET-1, and IL-6 are directly or indirectly activated by DEX treatment in the heart of preterm newborns. In turn, these molecules lead to a downstream signalling cascade that converges on an increased intracellular  $Ca^{2+}$  current. As evidence of this process, this cascade is inhibited by the calcium-antagonist nifedipine, capable of inducing regression of hypertrophy (89). The central role played by high levels of intracellular  $Ca^{2+}$  in the genesis of CCHC is to modulate the transcriptional activity in cardiomyocyte. Modifications of NFAT and myocyte enhancer factor-2 (MEF2) may induce hypertrophy through activation of foetal protein isoforms. The molecules mentioned previously, together with aldosterone and TGF- beta, are capable of activating pathways leading to modulation of the production of transcription factors such as nuclear factor kappa B (NF-



**Figure 1.** Possible pathway for the regulation of corticosteroid-induced hypertrophic cardiomyopathy is illustrated. A considerable number of stimuli, such as Ang-II (Angiotensin II), TGF-beta (Transforming growth factor beta), ET-1 (Endothelin 1), IL-6 (Interleukin-6) are directly or indirectly activated by DEX (dexamethasone). These molecules lead to a downstream signalling cascade that converges on an increased intracellular  $Ca^{2+}$  current. High levels of intracellular  $Ca^{2+}$ : a) modulate the transcriptional activity in cardiomyocyte (genes NFAT, MEF 2, NF-KB, AP- 1, SMADA, STAT), thus inducing hypertrophy, apoptosis and fibrosis b) acts on contractile and cytoskeletal proteins, producing cellular disarray

kB), activating protein-1 (AP-1), small mothers against decapentaplegic (SMADA), signal transducer and activator of transcription (STAT), which control activation / inhibition of MMPs and TIMPs (90).

It is likely that  $Ca^{2+}$  also acts on contractile and cytoskeletal proteins that play an important role in maintaining the normal structure of cardiomyocytes. As evidence of this, DEX-induced cardiac hypertrophy in newborn rats is accompanied by changes in desmin filaments, responsible for myocyte disarray in infant cardiac muscle following CCs treatment. The latter may predispose to impaired cardiac function, such as cardiac dilatation and heart failure, in later life (43,91). An increased number of desmin filaments characterized by a disordered arrangement in myocytes, has also been detected by means of immunoelectron microscopy in cardiomyocytes threatened by stress overloading in the diseased human heart (92). Findings of extreme interest have been obtained in a study performed to investigate the redistribution of cardiac myosin heavy chain (MHC) isoform. Myosin is a contractile protein found in the cardiac muscle. Northern blot and slot blot analysis

revealed that CCHC in newborn rats is accompanied by an increase in steady state level of alpha-MHC, mediated in part by means of a transcriptional mechanism, and decreased expression of beta-MHC in a dose dependent (93). A similar finding has been reported with regard to neonatal cardiac hypertrophy associated with diabetic pregnancy, in which alpha-MHC levels were increased, whereas beta-MHC were reduced. However, contrary to findings reported for CCHC, ANP levels were decreased (94). These data suggest that the system described may represent an effective model for use in the elucidation of cellular and molecular mechanisms implicated in the development of ventricular hypertrophy in infants receiving CCs therapy for bronchopulmonary dysplasia (Figure 1).

#### 4. SUMMARY AND PERSPECTIVE

The involvement of several pathophysiological mechanisms and biomarkers in the onset of hypertrophic cardiomyopathy in adulthood (both idiopathic and acquired forms) has been amply cited in literature; however, there is a relative scarcity of reports focusing on neonatal cardiac hypertrophy, particularly when induced by CCs

administration. As reported in the present review, multiple changes have been observed in the neonatal heart in response to CCs administration. Epidemiologic studies have led to the hypothesis of a foetal origin of the adult disease, maintaining that early lifestyle factors, imposed by intrauterine or neonatal environment, may increase the risk of developing cardiovascular disease and hypertension in later life (95). In particular, exposure to excess CCs during critical early life stages has been implicated as a factor that may program long-term changes in cardiac function, predisposing to adult disease (96). Perinatal programming describes the long-term adaptive changes that an organism undergoes in response to an early insult, such as the adverse effects elicited following neonatal drug administration. In this specific case, the term is applied to describe the increased incidence of adult disease, including cardiovascular disease, reported in literature in populations exposed to increased levels of CCs. These stimuli result in a variety of changes in cardiac function and gene expression, many of which persist into adulthood (21, 42). Findings obtained in the experimental studies reported here appear to question the safety of CCs administration to human neonates. If indeed the results obtained are applicable to humans, an early screening and cardiovascular follow-up program may be warranted to enable secondary prevention, particularly in adulthood (97). However, the cardiac hypertrophy manifested during DEX treatment of newborn rat pups is similar to that observed in premature infants treated with CCs (21). In conclusion, the study of biomarkers in experimental models and clinical studies of CCHC has provided further insight into the possible mechanisms implicated in producing adverse drug effects, although further studies are clearly required. Moreover, the study of biomarkers in animal models and infants affected by CCHC might help to identify molecules involved in the triggering of hypertrophy and/or fibrosis. These biomarker may prove to be of use in determining prognosis factors or progression of the disease subsequent to apparent remission. Finally, the study of biomarkers and their signalling pathways in CCHC might enhance the investigation of new therapeutic strategies with the aim of modifying the natural course of the disease.

## 5. ACKNOWLEDGEMENTS

Authors Pier Paolo Bassareo, Raul Abella, Vassilios Fanos and Giuseppe Mercuro equally contributed to this article. They gratefully thank Mrs Maria Leo who took care of iconography.

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**Abbreviations:** CCs: corticosteroids; CLD: chronic lung disease; NICU: Neonatal Intensive Care Units; DEX: dexamethasone; CCHC: corticosteroids-induced hypertrophic cardiomyopathy; TGF-beta: transforming growth factor-beta; RAAS: renin-angiotensin-aldosterone system; Ang-II: angiotensin II; NFAT: nuclear factor of activated T cells; TNF-alpha: tumour necrosis factor-alpha; TNF-beta: tumour necrosis factor-beta; cTnT: cardiac troponin T; ET-1: endothelin; ADMA: asymmetric dimethylarginine; vWf: von Willebrand factor; PAF:

## Corticosteroids-induced cardiac adverse effect

platelet-activating factor; PDGF: platelet-derived growth factor; TAT: thrombin - antithrombin III complex; F1+2: thrombotic prothrombic fragment 1 + 2; TGF-  $\beta$ : transforming growth factor-  $\beta$ ; IL-6: interleukin-6; ANP: atrial natriuretic peptide; BNP: B-type Natriuretic Peptide; NTpBNP: N-terminal-Pro-BNP; MMPs: matrix metalloproteinases; TIMPs: tissue inhibitor of matrix metalloproteinases; MEF2: myocyte enhancer factor-2; NF- $\kappa$ B: nuclear factor kappa B; AP-1: activating protein-1; SMADA: small mothers against decapentaplegic; STAT: signal transducer and activator of transcription; MHC: myosin heavy chain

**Key Words** Corticosteroids, Chronic lung disease, Hypertrophy, Cardiomyopathy, Preterm, Biomarkers, Review

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