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Non-Ultradian Cardiac Rhythms: Circadian Regulation of the Heart

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1. Introduction

The heart undergoes relentless biophysical oscillations over the course of a life span in order to sustain life. The heart's continuous rhythm of beating consists of sustained, serial oscillations in ionic currents, membrane potential, and excitation-contraction coupling. The rhythm of its beats expresses a period range of 0.6-1 seconds in healthy adults. These high frequency ultradian (< 24 hr period) rhythms are the life blood of the body's most important myogenic oscillator and pump. However, these are not the only rhythms vital to the function of cadiac tissue, as the heart and other components of the cardiovascular system are under control of the body's circadian clock. This "clock" is not a singular entity, but rather consists of distributed oscillators which impose numerous biochemical and physiological rhythms with a periodicity of approximately 24 hours. Indeed, recent evidence has demonstrated that the very cells of the heart are circadian oscillators themselves.

Numerous studies of animal models, including humans, reveal that multiple processes of cardiac physiology are under control by the circadian system. Moreover, circadian control by the organismal "clock" encompasses multiple layers of regulation, extending, at its most reduced level, to the molecular clockworks residing within individual cardiomyocytes (Bray et al., 2008) and other cardiac cell types (Young, 2009). Coupling between cardiomyocytes at the tissue level results in a synchronized cardiac organ-clock. The cardiac clock functions in a semiautonomous manner in isolation from autonomic and humoral inputs. These "exogenous" inputs represent regulatory arms of the larger circadian system to which the cardiac clock is subject to control. The neurohumoral arms of the circadian system are driven by the neurocephalic circadian axis, the most important component of which (at least in mammals) resides in the suprachiasmatic nuclei of the hypothalamus. However, other cephalic components, including the eye and pineal, reinforce central and peripheral oscillations and maintain coupling between them, as well as with true exogenous factors such as light and dietary intake (Bell-Pedersen et al., 2005; Stratmann and Schibler, 2006). Together, these multiple systems interact to produce overt rhythms in cardiac physiology including rhythms of heart rate, contraction force, blood pressure, metabolism, gene expression, and more (Young, 2009).

Of particular clinical interest is the observation that multiple aspects of cardiac pathology fluctuate on a circadian basis. Numerous studies have documented daily oscillations in the occurrence of pathologic cardiac events (Elliott, 2001; Mahmoud at al., 2011). The collective impact of these time-of-day-dependent phenomena on human welfare and

economics is likely enormous, though the etiology of this temporal dependence is not fully understood. Elucidation of the mechanisms underlying these time-dependent phenomena is no doubt complicated by the complex, hierarchical organization of the circadian system and its far-reaching presence across most tissues. In fact, it is not always clear what direct role circadian regulation plays in rhythmic features of cardiac physiology and pathology compared to indirect effects which may propagate between coupled organ systems. Moreover, not all such rhythms may necessarily be attributed to endogenous circadian control at all; rather, some rhythms may be driven independently by oscillating exposure to environmental factors themselves and not as zeitgebers (timekeepers or entrainment cues).

Understanding the role of the circadian system as a primary regulator of daily changes in cardiac physiology and pathophysiology is of both extreme scientific and clinical interest. Development of new therapeutic modalities, as well as improving standard ones, will require an unraveling of these intertwined regulatory processes, both direct and indirect, internal and external. This necessitates a deeper characterization of the role of circadian processes at multiple levels of cardiac function, from the cellular and molecular levels to the systems and organismal levels. The aim of this chapter, therefore, is to review the ever-increasing wealth of data on circadian control of the heart obtained from human and non-human animal models. I will explore many of the major findings to date at each hierarchical level of control to provide a broad view of how the circadian system regulates the physiology of the heart, contributes to its pathology, and adds to our current understanding of cardiovascular health.

2. The mammalian circadian clock

Circadian rhythms are defined as entrainable biological rhythms having an intrinsic periodicity under constant conditions (e.g. lighting conditions or temperature) of approximately 24 hours. Circadian clocks are ubiquitous amongst living organisms, and can be found across far-reaching taxa, including mammals, birds, lower vertebrates, invertebrates, non-animal multicellular organisms, and unicellular organisms (Bell-Pedersen et al., 2005). Among mammals, circadian clocks have been studied in numerous strains (both "normal" and pathological) of rodents, primarily in mice, rats, and hamsters, as well as other model systems, including humans (Martino and Sole, 2009).

These studies, along with studies of other vertebrate models (Bell-Pedersen et al., 2005), have demonstrated that numerous semi-autonomously operating clocks reside within a single mammalian organism. These clocks are distributed amongst most organs and tissues of the body, and can be reduced to the level of the individual cell (Stratmann and Schibler, 2006). These countless cellular clocks are biochemically coupled to produce coherent outputs at the tissue and organ levels, and govern a vast array of documented biochemical and physiological processes, including sleep-wake cycles, body temperature, metabolism, and cardiovascular functions to name a few.

2.1 Central physiological clocks

At the organismal level, central neural and peripheral clocks are organized in a hierarchical fashion, with intercellular communication being mediated by both neural and humoral mechanisms (Stratmann and Schibler, 2006). At the top of this hierarchy is the neurocephalic circadian axis, consisting of the hypothalamic suprachiasmatic nuclei (SCN) at its heart, along with the optic retinae and the epithalamic pineal gland (Bell-Pedersen et al., 2005).

The SCN, at the top of this neurohumoral triumvirate, is regarded as the "master pacemaker", as it synchronizes peripheral oscillators and dictates the appropriate phasing of "slave oscillators" subject to the regulatory arms of the central circadian axis. Consistent with the SCN's role as master pacemaker, its ablation abolishes multiple physiological and biochemical processes in multiple model species (Turek, 1985), and in rats loss of rhythms can be rescued by transplantation of intact SCN from donor rats (Ralph et al., 1990). Importantly, the period of host activity rhythms is imposed by the period of the donor animal in transplantation studies. Specifically, cardiovascular rhythms are under control of the SCN, as ablation of SCN abolishes rhythms in both blood pressure (Weaver, 1998) and heart rate (Warren et al., 1994) in rodents.

In vitro, individual cells of the SCN are capable of sustaining rhythms of multiple clock controlled outputs, including action potential firing rate, neuropeptide release, glucose uptake, and rhythms of gene expression (Bell-Pedersen et al., 2005; Quintero et al., 2003; Welsh et al., 1995). Intercellular coupling mechanisms within the SCN are unknown, though pathways coupling the SCN with other organs have been described. The SCN is part of a neuroendocrine feedback loop between the eyes and pineal gland, and these mutual interactions are necessary for entrainment or reinforcement of the hypothalamic clock.

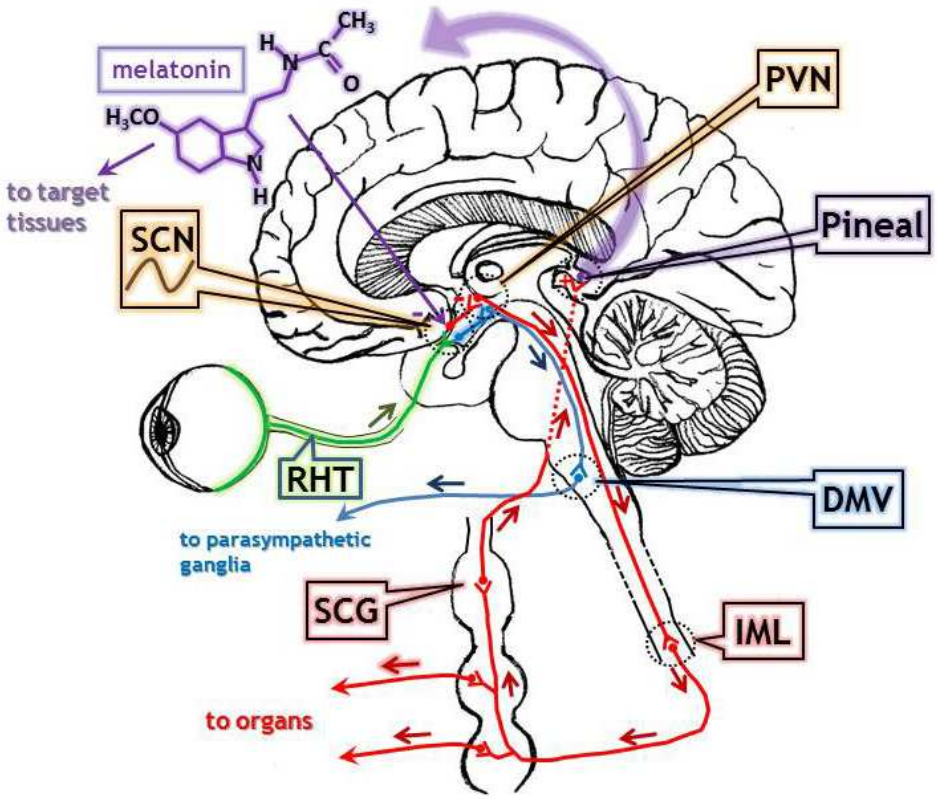

Fig. 1. Neuroendocrine pathways involving the SCN

As Figure 1 shows, light entrains the SCN via neural connections from the retinohypothalamic tract (RHT). In mammals, the SCN (and perhaps the retinae) is the only oscillator that is directly entrainable by light, although the pineal gland of many other vertebrate species is directly photoreceptive (Bell-Pedersen et al., 2005). The mammalian pineal, while not directly photosensitive, influences SCN activity by nightly secretion of the indoleamine hormone melatonin. The SCN is rich in melatonin receptors, and its activity is thus inhibited by melatonin during the dark period (Cassone et al., 1987). The neurohumoral feedback loop is closed by a polysynaptic pathway as follows. First order GABAergic neurons from the SCN synapse with neurons in the paraventricular nucleus (PVN) of the hypothalamus. Descending tracts from the PVN innervate targets in the intermediolateral cell column of the thoracic spinal cord, which in turn project to the superior cervical ganglia (SCG). Finally, sympathetic SCG neurons form noradrenergic synapses with the pineal gland, which possesses stimulatory β_2 adrenergic receptors (Moore, 1996).
The SCN regulates other peripheral organs (including the heart) by way of different autonomic efferents. In addition to sympathetic regulation by way of the IML, alternate SCN controlled efferent pathways arising from the PVN regulate parasympathetic ganglia by projecting to neurons in the dorsal motor nucleus of the vagus (DMV). It appears that separate populations of pre-autonomic cells in the SCN provide discreet control over symapathetic and parasympathetic pathways (Buijs et al., 2003).

2.2 Peripheral clocks

Previously it was believed that the master pacemaker within the SCN drove downstream oscillations in other tissues throughout the body, and that the molecular clockworks that underlie oscillator function were confined to this tissue. This view was largely based on studies which measured disruption of behavioural and physiological outputs of the organismal clock, and disruption of molecular rhythms in some tissues. It is now known that most tissues possess the same basic molecular machinery (i.e. "clock genes") as the hypothalamic pacemaker, and that many tissues (including the heart) can maintain functional oscillations in gene transcription and other processes in a semi-autonomous manner (Damiola et al., 2000; Oishi et al., 1998; Stratmann and Schibler, 2006).
Clock gene oscillations have been maintained in some peripheral tissues for periods of up to 20 days in culture, indicating a functional molecular clock is preserved *ex vivo* (Yoo et al., 2004). Other experiments have demonstrated that clock gene rhythms are not abolished in peripheral organs by SCN lesions, but that organs lose synchrony with one another, leading to altered phase relationships and disrupted coherent output *in vivo* (Guo et al. 2005, 2006; Yoo et al., 2004). Moreover, implementation of a restricted feeding paradigm (RF) competing with light cycles can uncouple rhythms in heart and liver from the SCN, without affecting the phase of the SCN itself (Damiola et al., 2000; Hara et al., 2001; Stokkan et al., 2001). As a result of these and other studies, the current prevailing view of the SCN as the body's circadian pacemaker is that its role is to synchronize, or entrain, functional peripheral oscillators throughout the body, rather than drive them directly.

2.3 Entrainment of peripheral clocks

As entrainable oscillators, peripheral tissues may be synchronized by neural or humoral signals, or by non-photic exogenous factors such as nutrient intake. Models using parabiosis between intact and SCN-lesioned mice demonstrate that some tissues, such as liver, can be entrained by humoral (or other non-neural) factors (Guo et al., 2005). Surpisingly, neither

implantation of SCN tissue grafts nor non-neural cues from parabiotically linked mice are sufficient to rescue clock gene rhythms in other tissues, including cardiac tissue (Guo et al., 2005, 2006).

Food intake is a powerful zeitgeber for some peripheral tissues including the heart (Balsalobre et al., 2000; Le Minh et al., 2001; Stratmann and Schibler, 2006), and the heart can be regulated in discordance with the SCN under a restricted feeding schedule. The mechanism of food entrainment likely involves metabolic feedback into the transcriptional clock gene cycles, which in turn regulate multiple metabolic processes (Koshaka and Bass, 2007). Cellular redox state is known to modulate transcriptional clock gene regulation, and this may represent one or more pathways by which feeding induced metabolic changes can regulate the heart and other clocks (Rutter et al., 2001).

Plasma glucocorticoid levels are rhythmic in mammals (Stratmann and Schibler, 2006), and glucocorticoid signaling interacts with metabolic entrainment (Le Minh et al., 2001). Moreover, glucocorticoids are capable of phase shifting molecular rhythms in cardiac tissue and other peripheral tissues (Balsalobre, 2000). Plasma levels of epiniphrine and norepinephrine (NE) also show diurnal rhythms in humans (Sauerbier et al., 1977), and NE can entrain circadian clocks within cultured rat cardiomyocytes (Durgan et al., 2005). Thus, glucocorticoids, especially cortisol in humans, as well as catacholamines, represent other potential zeitgebers for peripheral oscillators. These may provide important mechanisms by which the SCN exerts control over the heart and other tissues (Stratmann and Schibler, 2006).

Nightly melatonin secretion by the pineal represents another humoral regulatory arm of the circadian system, though extra-pineal contributions to plasma melatonin levels are not fully characterized in mammals (Huether, 1993). Interestingly, recent evidence demonstrates mammalian cardiac tissue possesses active biosynthetic machinery necessary to produce melatonin (Sanchez-Hidalgo et al., 2009), suggesting that extra-pineal melatonin derived from cardiac tissue may act as a local autocrine or paracrine signal.

Numerous beneficial cardioprotective effects have been reported for melatonin (Reiter and Tan, 2009). Cardiovascular tissues express both MT1 and MT2 melatonin receptors throughout the body, and cardiomyocytes express membrane bound melatonin receptors both *in vivo* and *in vitro* (Pang et al., 1993; Peliciari-Garcia et al., 2011). The nuclear melatonin receptor RORa has been localized to heart as well (Naji et al., 2004), and cardiovascular modulation of heart rate in primates may involve activation of intracellular MT3 receptor quinone reductase 2 (QR2) (Inui and Hazeki, 2010). Because melatonin exerts non-receptor mediated effects on target tissues as well (as a powerful anti-oxidant and scavenger of free radicals), it is unclear which cardioprotective mechanisms may involve receptor-dependent or receptor-independent regulation.

2.4 Cellular and molecular clocks

The mammalian intracellular circadian clock is composed of a finely tuned molecular feeback loop (Figure 2). The major components of this feedback loop consist of "clock gene" products that either activate expression of other genes (positive elements) or inhibit gene expression (negative elements). The primary positive elements are encoded by the genes *clock* and *bmal1* (*brain and muscle ARNT-like protein 1*); these gene products contain a basic helix-loop-helix Per-ARNT-Sim (bHLH/PAS) domain, which allow them to heterodimerize in the cytoplasm, after which they translocate into the nucleus to activate gene transcription. CLOCK:BMAL1 heterodimers activate transcription of target genes (including other "clock genes" as well as "clock controlled genes", or "ccg's") by binding to consensus E-box sequences in their promoters (Muñoz and Balor, 2003).

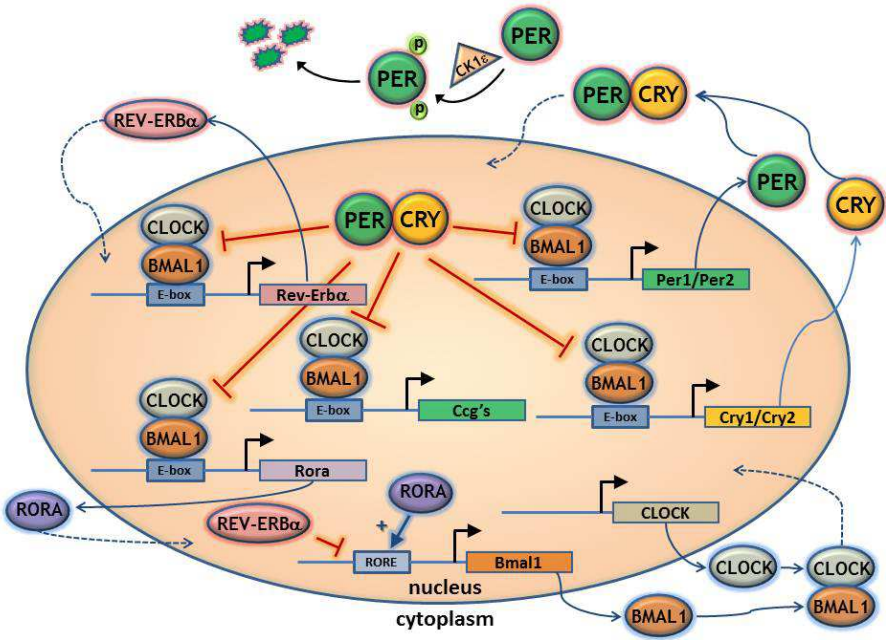

Fig. 2. Model of the intracellular molecular clock.

Two important targets of CLOCK:BMAL1 activation are the "negative" clock genes, *period* (*per*) and *cryptochrome* (*cry*). These phylogenetically conserved genes are preserved as core clock genes, although multiple mammalian orthologs of these genes have arisen as a result of gene duplications (Bell-Pedersen et al., 2005). Indeed, mammalian clock genes include three different *period* genes (*per1*, *per2*, and *per3*) and two *cryptochrome* genes (*cry1* and *cry2*). PER and CRY proteins heterodimerize in the cytoplasm and are then translocated into the nucleus, where they inhibit transcriptional activation by the CLOCK:BMAL1 complex. The negative elements close the loop, and robustness of the oscillations is enhanced by the positive limb. Accurate timekeeping is required to generate a ~24 hour period, and this requires precise timing of the feedback loop kinetics. This is mediated in part by the gene products of *casein kinase 1 epsilon* (*CK1ε*) and *casein kinase 1 delta* (*CK1δ*), which regulate stability and translocation of the PER:CRY complex via modulation of the PER phosphorylation state.

Redundancy is built into the circadian transcriptional loop by the presence of multiple functional isoforms of *period* and *cryptochrome* genes, as well as the gene for *neuronal PAS domain protein2* (*npas2*), whose protein product can substitute for CLOCK as a BMAL1 dimerization partner in some tissues (Reick et al., 2001). It is unclear what specific roles these partially redundant clock genes may have, however, and *per3* does not appear to be necessary for sustainment of the intracellular transcriptional oscillator (Ko and Takahashi, 2006). A fascinating study by Qi and Boatang showed that CLOCK protein localizes to the Z-disk of the cardiomyocyte sarcomere, and that translocation of CLOCK between the nucleus and cytoplasm is influenced by the activity of cross-bridge cycling (Qi and Boateng, 2006). Thus, cardiomyocyte activity may feed back into the core clock mechanism itself.

A secondary feedback loop is formed by activation of CLOCK:BMAL1 targets *rev-erbα* (an orphan nuclear receptor member) and *rora* (*retinoic acid-related orphan nuclear receptor*). REV-ERBα and RORA proteins competitively bind to retinoic acid-related orphan receptor response elements (ROREs) in the promotor of *bmal1*. These proteins have antagonistic functions, such that REV-ERBα represses *bmal1* transcription while RORA activates it. Furthermore, the kinetics of these protein activities differs, such that *bmal1* repression by REV-ERBα occurs more immediately, followed by a delayed activation by RORA (Ko and Takahashi, 2006). This secondary feedback loop is thought to stabilize the core transcriptional oscillator involving the *period* and *cryptochrome* genes (Preitner et al., 2002). Importantly, *rev-erbα* and *rora* genes have been shown to regulate pathways involved in cellular metabolism, which may have important consequences for cardiometabolic pathologies. These mechanisms are discussed in detail later. A third feedback loop (not illustrated) is based on transactivation of the *dec1* and *dec2* genes by the CLOCK:BMAL1 complex, followed by inhibition of CLOCK:BMAL1 by DEC1 and DEC2 proteins.

Most of this ensemble of clock genes has been shown to be rhythmically expressed in hearts of mammals and other animals (Cahill, 2002; Chong et al., 2003; Dardente, 2007), and clock gene mRNA rhythms have recently been measured in human hearts for *per1*, *per2*, and *bmal1*, but not *cry1*, which appears to be arrhythmic. (Leibetseder et al., 2009). Interestingly, the phases of clock gene mRNAs do not necessarily predict the phases of clock controlled outputs, and the phase angles between the core oscillator and outputs may be tissue specific (Karaganis et al., 2009).

Because the heart contains multiple cell types, including cardiomyocytes, epithelial cells, fibroblasts, and adipocytes, *in vivo* cardiac clock gene expression could reflect contributions of any one (or combinations) of these cell types. Indeed, functional clocks have been described in endothelia (Dermot et al., 2007; Takeda et al., 2007), adipose tissue (Zvonik et al., 2006), and fibroblasts (Welsh et al., 2004). However, rhythmic clock gene expression persists *in vitro* in isolated rat cardiomyocyte cultures (Durgan et al., 2005; Peliciari-Garcia, 2011), demonstrating the presence of a functional cardiomyocyte clock.

Intrerestingly, exogenously administered melatonin alters circadian expression of *rev-erbα* mRNA in rat cardiomyocyte cultures (Peliciari-Garcia et al., 2011). In addition to the membrane bound melatonin receptors, RORA has been described as a functional nuclear melatonin receptor, and may provide an important link between melatonin and regulation of peripheral oscillators, including the heart (Peliciari-Garcia et al., 2011). Other ROR members, including RORγ, may play in important role in peripheral oscillators as well (Ko and Takahashi, 2006).

2.5 The cardiac circadian transcriptome

Modern technology utilizing high density microarrays to report global gene transcription in murine models has tremendously expanded our understanding of the extent to which the circadian clock may regulate cellular function. Several laboratories have conducted microarray analyses to explore global cardiac gene expression in various normal and pathological murine models (Bray et al., 2008; Martino et al., 2007; Storch et al. 2002). The first such study to be conducted compared the circadian transcriptome between mouse heart and liver, and found that ~8% of cardiac genes (or 462 genes represented on the array) exhibited circadian oscillations (Storch et al. 2002). Other studies have yielded similar but more extensive estimates (up to 13% of heart genes rhythmic), or lower estimates (2-5% heart genes rhythmic) where greater stringencies were imposed on the analysis (Bray et al., 2008; Martino et al., 2007).

Gene ontology analysis from these studies reveals regulation across a wide array of molecular pathways, from genes involved in metabolism to cellular trafficking and cell death, to name a few. Surprisingly, although ~10% of genes were shown to be rhythmic in the liver (Storch et al., 2002), and these included similar functional gene categories as in the heart, there was very little overlap between individual genes showing circadian expression patterns in both tissues. In fact, only 39 genes showed similar circadian regulation in both heart and liver (Storch et al., 2002). This surprising result, along with microarray analyses of clock controlled transcriptomes in other tissues and organisms (Bailey et al., 2004, 2007; Duffield, 2003; Karaganis et al., 2008), have demonstrated that circadian regulation of gene transcription is both extensive and divergent. A key concept which has emerged from these studies is that circadian regulation of intracellular pathways is highly specific, and likely tuned to the particular demands and functions of a given tissue or organ. As we've seen, the heart is no exception.

Subsequent studies of murine cardiovascular tissue have confirmed and extended these observations, demonstrating that global regulation of clock controlled genes is divergent between closely related tissues or within different functional regions of the same organ (Bray et al., 2008; Martino et al., 2007). Separate analysis of rhythmic gene expression in atria and ventricles of mouse heart has demonstrated a surprising divergence in the apparent number of clock controlled genes expressed within these two tissues (Figure 3). In this study, which utilized mutants with cardiomyocyte specific clock disruption to identify intrinsically regulated ccg's (more on this later), 548 genes exhibited circadian transcriptional rhythms in the atria, compared to 176 genes in the ventricles (Bray et al., 2008).

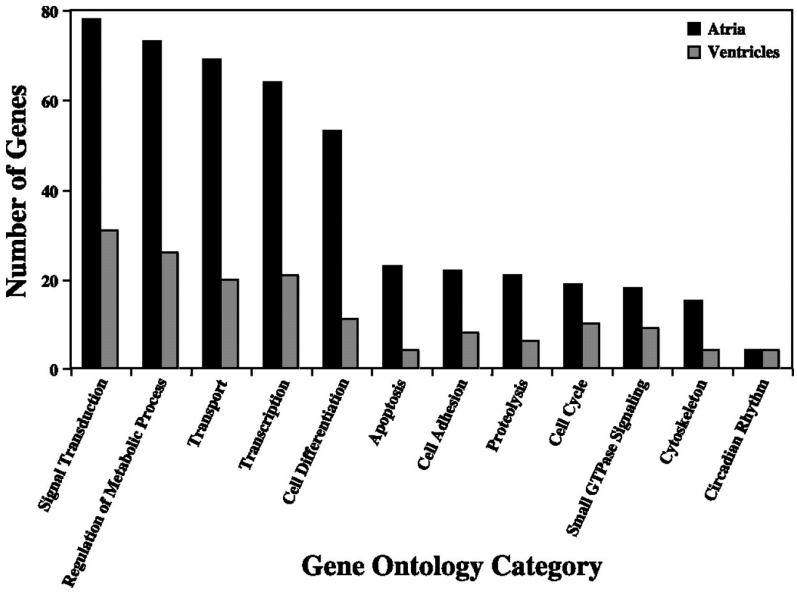

Fig. 3. Gene ontology of circadian regulated genes from atria and ventricles. From: Bray, et al., (2008). Disruption of the Circadian Clock Within the Cardiomyocyte Influences Myocardial Contractile Function, Metabolism, and Gene Expression. *American Journal of Physiology. Heart and Circulatory Physiology, Vol.* 294, pp.H1036–H1047, ISSN 1522-1539

Many of these genes could be expected to influence normal and pathological aspects of cardiophysiology, including genes affecting metabolism, contractile function, and cell growth or remodeling. It is worth mentioning a word of caution when interpreting the functional significance of these studies, however, since the behaviors of oscillating transcripts do not necessarily predict that final gene products will have similar protein expression profiles. Posttransciptional and posttranslational regulatory mechanisms, such as phosphorylation and ubiquitination may also be under clock control. The final relative phasing and amplitudes of protein expression may therefore arise from a complex interplay between regulatory pathways involving kinetics of gene transcription and translation, as well as mRNA and protein turnover via stability and degradation pathways. This point is highlighted by an important study conducted by the Hastings lab, which discovered extensive differences between circadian regulated transcription and protein levels in the mouse liver (Reddy et al., 2006). For instance, this study revealed that up to 20% of the hepatic proteome was rhythmic, while mRNA levels were rhythmic for less than half the number of these genes. Clearly, circadian regulation at the transcriptional level is an important mechanism of regulation by tissue clocks, but caution must be taken when extrapolating these findings to the protein level.

3. Circadian cardiovascular physiology and pathology

The circadian system regulates numerous cellular and molecular processes of cardiovascular function, including blood pressure, heart rate, contractility, vasomotor tone, blood clotting, and cardiovascular metabolism (Sole and Martino, 2009). It is presumed that normal function of these processes is necessary to maintain optimal health and longevity, and that disruption of circadian regulation of these processes can lead to both acute and chronic pathologies, some with potentially disastrous consequences. This section will describe some of the major features of cardiovascular function and pathology that may be regulated by the circadian clock.

Because other rhythmic environmental exposures and behaviours may drive physiological rhythms with similar periodicities maintained by the circadian clock, it is possible that some ~24 hour cardiovascular rhythms are not a result of circadian control (i.e., are not endogenously maintained rhythms). Moreover, because of the hierarchical organization of the organismal circadian system, measurable outputs may reflect different levels of control, ranging from local intrinsic oscillator function to systems level control by the neurohumoral arms of the SCN and other components of the circadian system.

Indeed, it is likely that many rhythmic processes of the cardiovascular system reflect combinatorial interactions between multiple oscillating systems, both intrinsic and extrinsic. For instance, platelet aggregability, a likely predisposing factor for acute ischemic cardiovascular incidents, is elevated as a result of morning standing and ambulation, but is not increased in the absence of morning activity (Andrews et al., 1996; Brezinski et al., 1988). In contrast, other predisposing factors for cardiac ischemia, such as oscillating fibrinolytic activity of endolthelial cells, may be regulated by circadian oscillators both intrinsic and extrinsic to the heart (Maemura et al, 2000).

3.1 Temporal variation in the timing of acute cardiovascular events

Several acute types of pathological cardiovascular events present in a circadian fashion. For example, the incidence of myocardial infarction in humans is much higher in the morning

hours, peaking between 06:00-12:00, just as patients arise from bed, or soon before or after doing so (Cohen et al., 1997; Muller et al., 1985). In contrast, the incidence of infarcts reaches a nightly trough during the hours between 03:00-06:00. Overall, infarcts are approximately three fold more likely to occur during the morning than during night.

Other related cardiovascular events that peak in the early or late morning hours include deadly ventricular arrhythmias (Tofler et al., 1995), defibrillation threshold (Venditti et al., 1996) atrial and ventricular refractoriness (Kong et al., 1995; Simantirakis et al., 2001), ischemic stroke (Argentine et al., 1990), rupture of aortic aneurysm or aortic dissection (Manfredini et al., 2004; Mehta et al., 2002; Sumiyoshi et al., 2002) and sudden cardiac death (Mahmoud at al., 2011; Muller et al., 1987). Some cardiovascular events, such as atrial arrhythmias (Deguchi et al., 2009; Sandberg et al., 2010) or thromboembolic stroke (Marshal, 1977) may peak at other times of day. Comorbid conditions, such as obstructive sleep apnea (OSA), may influence the timing of cardiovascular events, and contribute to pathological circadian disruption (Kuniyoshi et al., 2008).

3.2 Circadian regulation of heart rate and blood pressure

Heart rate (HR) and blood pressure (BP) both exhibit diurnal rhythms in humans, peaking the during the day when humans are active, or during the active nocturnal phase in rodent models (Mansoor et al., 1994; Millar-Craig et al., 1978; Reilly et al., 2007; Weber et al., 2002). HR and BP are lowest during nighttime, but begin to rise in the early morning hours in anticipation of waking. These rhythms coincide with rhythms in autonomic tone, with the sympathetic system dominating during the day, and the parasympathetic system dominating at night. The adaptive value of these daily rhythms is obvious, in that elevated HR and BP allow the body to carry out the physical demands associated with daily activities, while a nightly reduction in the levels of these processes allows the sleeping body to save energy and shift its focus to other important demands, such as cellular upkeep, tissue remodelling, or other restorative processes (Sole and Martino, 2009). Importantly, the timing of these cardiovascular rhythms is slightly phase advanced relative to the sleep/wake cycles (i.e. cardiovascular rhythms anticipate transitions between activity phases), allowing for a smooth transition between these alternating states.

The importance of maintaining these diurnal cardiovascular rhythms is evident when comparing variants of hypertensive patients, known as “dippers” and “non-dippers”. In some hypertensive patients (“dippers”), normal amplitude circadian rhythms are maintained, albeit over an elevated baseline. Other hypertensive patients, so called “non-dippers”, express a continuously high blood pressure through the active and sleep phases. This latter group, having disrupted blood pressure rhythms, are at greater risk for developing other cardiovascular diseases and suffering organ damage (Mancia and Parati, 2000; Verdicchia et al., 1990, 1993). Classification of hypertensive patients as non-dippers is based on having less than a 10% decrease in blood pressure at night, since most normotensive patients exhibit a >10% change. Some studies, however, have shown that blood pressure rhythm amplitudes are distributed normally throughout a given population, indicating that a 10% threshold is an arbitrary cutoff value (Mancia and Parati, 2000).

Other important, related cardiovascular changes exhibit daily rhythms as well, including vascular resistance and tone, although studies have produced conflicting results about how vascular resistance changes throughout the day (Elherik et al., 2002; Kawano et al., 2002; Otto et al., 2004; Shaw et al., 2001), and differential, tissue specific vasomotor control may occur throughout the body.

4. Evidence linking cardiovascular rhythms and pathology with intrinsic oscillators

It is unclear to what extent daily variations in heart rate and blood pressure are due to intrinsic cardiac oscillators or exogenous factors. Because peripheral vascular clocks have been described (Dermot et al., 2007), and given the presence of circulating zeitgebers (Guo et al., 2004), it is possible that many rhythms of normal and pathological cardiovascular function can be attributed to these dispersed signals or to behavioural patterns. Until recently, diurnal rhythms in acute cardiovascular events have been attributed solely to the stress of awakening and the accompanying morning surge in blood pressure. In light of the discoveries of intrinsic cardiovascular clocks, however, these phenomena are currently being re-examined, and it is now clear that at least some of these diurnal pathologies result from a contribution of local, intrinsic circadian regulation.

4.1 Lessons from clock mutants

Several studies have shown disrupted cardiovascular rhythms in animal models possessing mutations in core clock gene components. For example, heart rate (HR) and arterial blood pressure (BP) rhythms (assayed by radiotelemetry) are abolished in *bmal1* knockout mutants (*bmal1*$^{-/-}$) even a under light:dark (LD) cycle, and *bmal1*$^{-/-}$ mice are hypotensive (Curtis et al., 2006). On the other hand, dominant negative *clock*$^{\Delta 19}$ mutants express a less severe phenotype, showing partial disruption of HR and BP rhythms (Curtis et al., 2006). Disruption of the negative limb of the core molecular clock also disrupts cardiovascular rhythms, as baseline rhythms in HR and BP (measured by vascular pressure transducers) were lost in both *cry1*$^{-/-}$ and *cry2*$^{-/-}$ mice under free-running conditions in constant darkness (Masuki et al., 2005).

Because these mutants have deficient clocks in all tissues, including the SCN, it is impossible to determine through these studies whether loss of intrinsic cardiac oscillators contribute to these phenotypes. To resolve this issue, ME Young and colleagues have generated mutant mice containing a cardiomyocyte-specific *clock*$^{\Delta 19}$ mutation, called CCM mice. By comparing various measures of cardiac function and global gene expression between wild type and CCM mice *in vivo* and *ex vivo*, this group has identified multiple putative pathways through which the intrinsic cardiomyocyte clock might regulate cardiovascular function and dysfunction (Bray et al., 2008; Durgan et al., 2006).

For example, *in vivo* heart function is altered in CCM mice, which show diminished HR rhythms, sinus brachycardia, reduced cardiac output, and other functional differences (Bray et al., 2008). Experiments utilizing an *ex-vivo* cardiac perfusion system demonstrate the normal heart undergoes circadian rhythms in cellular metabolism and contractile function in response to cardiac workload (Durgan et al., 2007). CCM mice show abolished rhythms in triglyceride synthesis, reduced cardiac efficiency, and chronically elevated fatty acid oxidation (Bray et al., 2008). Additionally, while normal hearts exhibit an increased responsiveness to fatty-acids during the active period, which persists *in vitro*, this rhythm is abolished in CCM hearts (Durgan et al., 2006). In agreement with this role of the cardiomyocyte clock as a regulator of cellular metabolism, genes regulating both lipid and glycogen metabolism where found to be regulated by the cardiomyocyte clock (Bray et al., 2008), and cardiac responsiveness to a high fat diet is altered in CCM mice (Tsai et al., 2009).

A working model proposed by Young and colleagues is that the cardiomyocyte circadian clock gates lipid metabolic pathways to balance β-oxidation rates with fatty acid supply in a

manner that is appropriate to the time of day. During the active period, when metabolic energy requirements are high, transcriptional responsiveness to fatty-acids is increased, allowing induction of triglyceride synthesis and fatty acid oxidation. This allows the heart to accommodate diurnal changes in circulating fatty-acids levels as a result of feeding or fasting status. This elevated transcriptional response at a time of day when fatty acid levels are high is necessary, since excess fatty acids can otherwise be shunted into harmful "lipotoxic" pathways. Thus, exposing the heart to an excess of lipids at an inappropriate time of day (when the transcriptional machinery is not primed for healthy lipid metabolism) can cause contractile dysfunction, as in diabetes mellitus (Young et al., 2002).

Interestingly, *rev-erbα* is known to be an important regulator of lipid metabolism, in addition to its role as a core clock gene (Duez and Staels, 2008). It functions to control intracellular triglyceride metabolism and β-oxidation pathways as well as plasma lipid and lipoprotein metabolism. Additionally, *rev-erbα* is implicated as a mediator of vascular inflammation, and has been speculated to play a role in the development of metabolic disorders, including obesity and diabetes. *Rev-erbα* could therefore contribute to the development of cardiovascular pathologies through multiple levels of control

4.2 Disruption of circadian cycles has cardiovascular consequences

Shift work has long been hypothesized to be a risk factor for cardiovascular disease and other chronic conditions in humans. Shift workers develop a non-dipper blood pressure profile and may be at increased risk for hypertension (Mosendane, 2008). Additionally, increased risk for metabolic disturbances have been reported for shift workers, including dyslipidaemia, metabolic syndrome, and diabetes, although a recent thorough review shows epidemiological evidence for metabolic and cardiovascular disease is inconsistent (Wang et al., 2011). However, the suggestive evidence warrants further study of these associations. The etiology of cardiovascular disease in shift workers, if present, is unknown. While there are many confounding factors associated with shift work (such as poor diet and higher smoking prevalence), circadian dyssynchrony has logically been proposed as a causative factor.

Several experimental animal studies support the hypothesis that circadian system perturbations cause or exacerbate cardiovascular disease and reduce longevity. In one such study, cardiomyopathic Syrian hamsters (a model for congestive heart failure) were subjected to weekly reversals of LD cycles, resulting in major disruptions of circadian body rhythms (Plamen et al., 1998). Rhythm-disturbed animals experienced a median 11% decrease in life span compared with controls.

Hamsters heterozygous for the *tau* mutation (a point mutation in the *CK-1ε* gene) have shortened periods and are unable to entrain properly to a normal 24 hour LD cycle. Fascinating studies have revealed that +/*tau* mutants have reduced longevity under a standard photoperiod, and longevity can be rescued in aged hamsters where normal SCN tissue has been grafted into the mutant host (Hurd and Ralph, 1998; Ralph and Menaker, 1988). Interestingly, *tau*/*tau* homozygotes are spared these deleterious effects as they cannot entrain at all under these conditions and can simply free-run. This observation demonstrates that internal desynchronisation of the circadian clock, and not the *tau* mutation *per se*, has pathological consequences.

A compelling recent study has demonstrated that mortality in rhythm perturbed +/*tau* hamsters coincides with major cardiomyopathy and renal disease (Martino et al., 2008).

Moreover, +/*tau* animals raised in a shorter photoperiod matching their endogenous period phenotype were protected from these deleterious effects, and were clinically no different than wild type animals. In addition, this research group showed that lesion of the SCN in young mutants protected mice from the onset of pathological cardiac hypertrophy under a disruptive light cycle. Collectively, these results provide powerful evidence that internal dissonance from the SCN pacemaker is harmful, and indeed worse than complete loss of the pacemaker itself.

Another study by Martino et al. compared global rhythmic gene transcription in heart and aorta in normal (sham operated) mice with those in an induced cardiovascular disease state (Martino et al., 2007). The rhythmic heart transcriptome was biphasic, as described elsewhere (Bray et al., 2008), and was highly similar to the aortic transcriptome, with an overall conserved phase angle, but somewhat phase delayed (Figure 4).

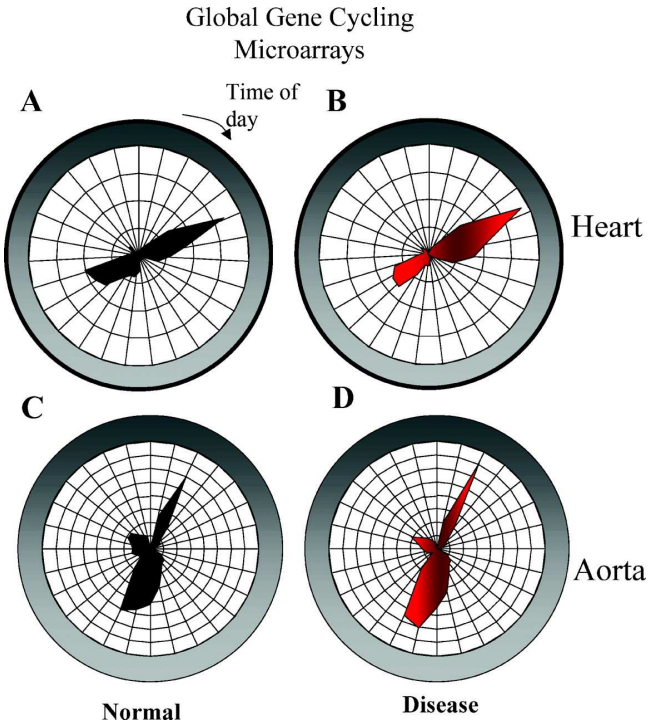

Fig. 4. Phase plots of circadian transcriptomes in heart and aorta. Reprinted from: Martino, et al., (2007). Disturbed Diurnal Rhythm Alters Gene Expression and Exacerbates Cardiovascular Disease With Rescue by Resynchronization. *Hypertension*, Vol.49, pp.1104-1113, ISSN 1524-4563

Remarkably, pressure overload induced hypertrophy (via transaortic constriction, or TAC) had no apparent effect on global circadian gene transcription in either the heart or aorta. However, TAC mice subjected to disruptive photoperiods exhibited abnormal adaptive responses to the disease state, such as vascular thinning and muscular atrophy as opposed to compensatory hypertrophy in the non-disrupted cohorts. Rhythm disturbed TAC mice

also exhibited altered cardiac rhythms of genes important for regulating hypertrophy, blood pressure, and fibrosis, as well as altered clock gene rhythms in both the heart and SCN. Furthermore, a rescue protocol implementing a restorative photoperiod reversed pathological loss of compensatory responses including cardiomyocyte hypertrophy and perivascular fibrosis (Martino et al., 2007). Therefore, it must be concluded that the circadian clock regulates compensatory cardiac tissue remodeling secondary to the primary cardiovascular disease state.

5. Therapeutic implications and future directions

5.1 Preventative chronotherapeutic applications

Our expanding current understanding of the circadian system's role in regulating cardiovascular function should, in principle, open new avenues for chronotherapeutic applications. Perhaps the simplest application is chronobiological awareness. All patients, and especially those with predisposing health risk factors, may benefit by practicing good "sleep hygiene". This refers to maintaining a regular sleep/wake schedule by going to bed and rising at regular times, and ensuring a full night's sleep. Patients should be screened for sleep apnea, which of course should be treated if found.

Unnecessary phase shifts, for instance due to traveling or late nights out, should be minimized. Re-entrainment after disruptive phase shifts, as in jet lag, can be facilitated using supplemental melatonin. This may be especially beneficial in frequent travelers. New melatonergic agonists, such as, *ramelteon* and *tasimelteon*, have different pharmacological properties and may provide alternative therapeutic effects. (Singh et al., 2010). The availability of alternative treatments offers the promise of individualized chronotherapies.

If at all possible, shift work should be avoided in patients with cardiovascular disease or with strong predisposing factors. If changing hours is not permissible, negative effects might be mitigated by chronobiological awareness and focus on making healthy pro-active lifestyle choices, such as maintaining proper diet and exercise regimes and undergoing regular physical exams. While these are good general preventative recommendations for any patient, a greater appreciation for the health benefits of circadian chronosynchrony may increase compliance, and can be aided by both an increase in doctor awareness and patient education.

5.2 Chronotherapeutic interventions

Multiple recent studies have shown a strong time-dependent efficacy for administration of anti-hypertensive medications, including beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARB's) (Takeda and Maemura, 2010). Chronotherapy was shown to be especially useful in patients with resistant hypertension, and more beneficial than changing drug combinations (Hermida et al., 2008). Anti-hypertensive chronotherapy, in conjunction with the benefits of ambulatory blood pressure monitoring in candidate patients (Mancia and Parati, 2000), could provide effective new means of tailoring treatment to subjects with different blood pressure profiles.

Chronic nightly melatonin administration has also been reported to reduce hypertension in human male patients (Scheer et al., 2004). In addition to its acute soporific, phase-shifting, and anti-hypertensive effects, melatonin has powerful cardioprotective benefits. This may be due in part to melatonin's properties as a potent anti-oxidant, but studies using a

perfused rat heart system have demonstrated a possible receptor dependent protection against ischemia/reperfusion injury (Genade et al., 2008). Clinical trials are underway to test the effectiveness of melatonin in treating human patients with ischemic heart disease (Dominguez-Rodriguez, 2007; 2010).

Mechanisms underlying circadian variation in cardiac arrhythmias are not understood, and chronotherapeutic studies for treating cardiac arrhythmias are lacking. However, circadian expression of voltage gated K^+ channel mRNA and protein levels (for *Kkv1.5* and *Kv4.2*) has been detected in rat heart (Yamashita et al., 2003), and more recently for L-type voltage gated Ca^{2+} channels (*VGCCa1C* and *VGCCa1D*) in embryonic chick heart (Ko et al., 2010). As we gain new understanding of how the cardiomyocyte circadian clock gates electrophysiological membrane properties, the way will be paved for the development of new chronotherapies targeting cardiac arrhythmias.

Perhaps the ultimate frontier of circadian chronotherapy lies in gene transfer techniques. Although current gene transfer methods are inefficient and risky, the field of gene therapy is in its infancy, and should be expected to mature as technical difficulties are resolved. Several labs have already employed these methods to treat hypertension in rat models, and other models of gene chronotherapy for the treatment of cardiovascular disease are under development (Lin et al., 1995, 1998; Murakami et al., 1999; Wang et al., 2004; Yla-Herttuala, 2000).

5.3 Future avenues of research

Much has been learned about the intimate partnership between circadian oscillators and cardiovascular health, and much is still to be learned. Fruitful avenues of research have employed circadian mutants, animal disease models, and a variety of *ex vivo* and *in vivo* preparations. Classical circadian research methods, such as surgical grafting, ablation, and cycle disruption, have been used to great new effect, in concordance with modern molecular tools such as mutant construction, and microarray analysis. This multi-pronged approach has revolutionized our understanding of peripheral oscillators, and energized a new paradigm for studying systems biology.

These same approaches and model systems will no doubt continue to produce valuable new knowledge, while advanced technologies promise to forge new inroads in the quest to unravel cardiovascular clocks. Adaptations of molecular manipulation techniques will allow valuable tissue specific knockdown and overexpression experiments to be conducted in parallel with genetic knockouts. Tissue and cell specific genetic engineering, side by side with improved biological assays, should allow us to continue to dissect the circadian code, gene by gene, protein by protein. The circadian proteome must be characterized and reconciled with the mosaic of divergent circadian transcriptomes. As new therapies are investigated, and epidemiological data are collected, we will continue to bridge the gap between laboratory animal and human patient.

6. Conclusion

As we've seen in this review, circadian rhythms are woven into the dynamic fabric of temporal cardiac homeostasis. Governance of this complexly balanced tapestry is shared between a synchronous cooperation between distributed, intrinsic oscillators and the master pacemaker within the SCN. Discordance between system components can cause cardiovascular dysfunction, and exacerbate pre-existing disease. While we continue to

unmask the role of circadian rhythms in cardiovascular function, the impetus will increase for application of circadian principles into clinical practice. As our fourth dimensional view of human medicine matures, we will more clearly see how circadian regulation of the heart is an indispensable feature of healthy cardiovascular function.

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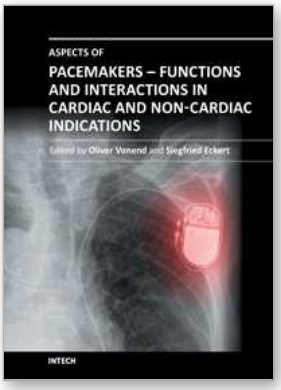

Aspects of Pacemakers - Functions and Interactions in Cardiac and Non-Cardiac Indications

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Outstanding steps forward were made in the last decades in terms of identification of endogenous pacemakers and the exploration of their controllability. New â€œartificalâ€ devices were developed and are now able to do much more than solely pacemaking of the heart. In this book different aspects of pacemaker â€“ functions and interactions, in various organ systems were examined. In addition, various areas of application and the potential side effects and complications of the devices were discussed.

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