Firefighting has long been known as a dangerous profession. Most research investigations of the deaths of first responders focus on the traumatic line-of-duty deaths and the higher incidence of cancer later in life. However, nearly half of on-duty deaths actually have cardiovascular causes. While some of this can be attributed to increasing rates of obesity in the fire service, there are also large numbers of young, otherwise healthy firefighters dying of heart complications, as well as reports of unusual arrhythmias in older firefighters. This realization prompted further investigation into the effect of under-recognized cardiac stressors in this high-pressure profession.

I am one of those clichéd medical students who has wanted to be a doctor since childhood, and having finally made it to medical school is a dream come true. That being said, I will go to my grave insisting, as my father and so many others do, that firefighting is the best job in the world. The four years I spent getting up at 2:00 AM to the beeps of a loud pager, driving huge red trucks around town, and running into buildings everyone else was running out of were some of the most meaningful years of my life, having taught me a great deal about life, teamwork, and accountability. But each of those years came at a cost, and it may be decades before I know just how high that cost will be.

My father was a career firefighter for 13 years. While he also claims that those were the best years of his life, he has begun to see the health costs of firefighting. In the last few years, he has started to make regular trips to funerals, first for his chiefs, now for some of his officers, and soon for his crewmembers. He says some members of his old engine company envy him, as they can see their own clock ticking after a much longer firefighting career, and they think he got out in time. For older firefighters, attending funerals can almost become part of the job. While many people might imagine that these firefighters died from complications of cancer, it is not that simple.

Recently, my father has been considering a cardiac ablation procedure for recurrent premature ventricular contractions (PVCs). After his cardiologist ran a whole battery of tests uncover the root cause of the PVCs, he simply told my father that this is something cardiologists always seem to see with firefighters later in life. If these arrhythmias were to occur in most other people, a physician might push harder to address them, but with firefighters they are just another consequence of a job well done. My father and I have often traded stories and hearsay about what might be causing firefighters to have such problematic hearts later in life. People on the job have blamed the lack of sleep, the repeated hits of adrenaline, and the harsh wakeup produced by loud pagers—but those were all just theories. So, I decided to take a close look at the scientific literature for some hard answers. Unfor-
tunately, while there is plenty of literature on cancer in firefighters, research on the effects of decades of adrenaline, stress, and interrupted sleep on the cardiac health of firefighters is scarce. What evidence does exist, however, is quite intriguing.

Cancer gets most of the attention in research on health complications in firefighters, but cardiovascular disease is what is really killing them. A CDC analysis from 2004 found that over 45% of on-duty firefighter deaths were caused by cardiovascular disease, and the proportion is not improving over time [1,2]. The majority of investigations into the cardiac health of firefighters have either focused on the chronic effects of obesity on cardiovascular health or the effects of acute firefighting stressors on cardiovascular health.

Obesity has well-documented impacts on cardiovascular health in the general population. It is associated with increased systemic inflammation, endothelial dysfunction, and resulting atherosclerosis, and it increases the risk of hypertension, heart attack, and stroke [3]. There has long been strong evidence of both immediate and long-term health benefits of weight loss [4]. The rising rates of obesity in the fire service could account for a large portion of cardiovascular-related deaths, but this does not explain why a large population of firefighters who are young, fit, and have not yet accumulated a substantial vessel disease burden, are also dying from cardiovascular events.

To understand what could contribute to the deaths of these young, fit firefighters, I looked into the cardiovascular consequences of vigorous exertion, like that required of those working on the fire scene. One study that analyzed high-level athletes showed that the risk of sudden cardiac death increases 2- to 3-fold during extreme physical exertion [5]. In line with this finding, firefighters are at
remarkably increased risk of death during physically stressful fire suppression activities (RR 22.1) [6]. In fact, the work during fire calls is strenuous enough to induce substantial clotting changes in firefighters even after 2 hours of recovery [7]. Both immediately after fire suppression activities and after 2 hours of recovery, firefighters had substantially increased platelet numbers, activity, and coagulation potential, along with a decreased partial thromboplastin time. Fibrinolysis was initially increased, but this increase was not maintained for as long as the increased clotting potential, which could help to explain some of the increased risk of cardiovascular death in the hours following strenuous emergency calls as their clotting systems fell out of balance.

The changes induced by physical stress, however, do not explain the increased cardiovascular risk associated with the many emergency calls that do not require strenuous physical activity. When considering other unusual aspects of firefighting that could explain this increased risk, long shifts and frequently interrupted sleep come to mind. One study found that firefighters who reported working sixteen 24-hour shifts in the last month had an average 5.0 mmHg higher diastolic blood pressure compared to those who reported working eight to eleven 24-hour shifts in the last month [8]. This raises the possibility that an intense firefighting schedule creates chronic stress on the cardiovascular system. Another study found that firefighters who were sleep deprived (getting 4 hours versus 8 hours of sleep) had significantly elevated cortisol levels, particularly in the afternoon and evening [9]. Given that getting 4 hours of sleep is the norm for firefighters, there is a need for more in-depth research into the effect of disrupted circadian rhythms, sleep deprivation, and increased cortisol levels on cardiac health in this population.

There are limited studies of the molecular regulation of circadian rhythms in humans, but an impressive molecular clock has been shown to drive circadian rhythms in mammals. This clock is driven by core-clock genes Bmal1, Clock, Per1/2, and Cry1/2. These genes work through a cyclic mechanism, whereby BMAL1 and CLOCK dimerize, activating PER and CRY. The accumulation of PER and CRY gene products then inhibits BMAL1:CLOCK activity [10]. This feedback loop is essential to regulating many clock-controlled genes. By immunoprecipitation analysis, the BMAL1:CLOCK complex binds at more than 2,000 sites across the genome in liver tissue [11]. Studies in mice have shown that knockouts of various molecular clock genes predispose mice to accelerated aging; increased cancer risk; hyperlipidemia and insulin insensitivity; and, in the case of Bmal1 knockout mice, dilated cardiomyopathy. Disrupting circadian rhythms in skeletal muscle led to dysfunction in sarcomere arrangement and decreased force production, along with decreased mitochondrial volume and increased respiratory uncoupling [11]. The disruption of circadian rhythms also changed muscle fiber type, causing a notable shift towards oxidative fiber types and reduced glucose uptake. While these are mouse studies, it is interesting to consider the whether these impacts could also be present in humans as well, and in firefighters in particular. If the phenotypes are even remotely consistent, disrupted sleep patterns could be predisposing firefighters to diabetes and obesity, resulting in downstream cardiovascular problems. Additionally, skeletal muscle dysfunction and decreased force production could put firefighters at greater risk during strenuous physical activity.

Furthermore, there is evidence that the effects of disrupted circadian rhythms go far beyond skeletal muscle changes. As it turns out, the gut also has its own peripheral circadian clock. While this clock can operate independently of the central circadian clock, it is generally synchronized with the other molecular clocks in the body. The gut clock is primarily regulated by the time of eating (and firefighters love to eat after getting back from a call at 3:00 AM). One group found that environmental circadian rhythm disruption can cause intestinal microbiota dysbiosis in both mice and humans, particularly when combined with dietary stress like a high-fat diet or alcohol consumption [12]. The study found an increase in pro-inflammatory microbiota that put the host at risk for immune dysfunction. Another study transferred intestinal microbiota from jet-lagged and non-jet-lagged humans into germ-free mice and found that the mice with bacteria from jet-lagged humans developed obesity and
glucose intolerance not seen in the control mice [13]. While mouse studies may not translate perfectly to human physiology, these results raise interesting points. The dysrhythmic eating patterns of firefighters may predispose them to dysbiosis favoring pro-inflammatory microbes, thus making them more likely to experience metabolic syndrome. Thus, they would not only be predisposed to obesity and diabetes but also to systemic gut inflammation that increases the risk of developing atherosclerosis, further contributing to the high rate of cardiovascular disease.

While there are a number of ways in which disrupted circadian rhythms could indirectly impact the cardiovascular system, a direct impact is also possible. A study of the circadian rhythmicity of Kruppel-like factor 15 (Klf15), a protein associated with metabolism and cardiac hypertrophy in cardiac tissue, showed that the Klf15 gene is transcribed in a dose-dependent manner in response to the Bmal1/Clock complex [14]. In addition, the Klf15-dependent transcription of KChIP2 played a key role in rhythmic variation in cardiac ventricle repolarization and susceptibility to arrhythmias and sudden cardiac death. In another study, the molecular clock in cardiomyocytes was found to regulate the expression of Kcnh2, which encodes a potassium channel important for normal ventricular repolarization [15]. Additionally, disruption of the circadian clock led to an unmasking of long QTc intervals in the light phase that were not seen in normal mice. While speculative, this phenomenon suggests a novel factor that puts firefighters at an increased risk for cardiovascular disease. There are many LED lights involved in emergency responses, and evidence suggests that these lights are quite effective.
at confusing the normal light-dark cycle. If firefighters are already prone to arrhythmias due to disrupted circadian rhythms, being forced abruptly into an artificial light phase, coupled with the intense adrenaline stimulation associated with every call, could put them at a substantially elevated risk of arrhythmias. Taken together, these studies provide some concerning evidence that disruption of the molecular clock can lead to an increased risk of arrhythmias and sudden cardiac death. However, more investigation with human studies is needed.

Altogether, the significantly increased risk of death secondary to cardiovascular disease in the firefighter population has a multitude of potential causes, including several beyond the obvious. Obesity and chronic stress may play large roles, but emerging evidence also points to the hazard of disrupted sleep cycles. There is increasing evidence that disrupting the finely tuned central and peripheral circadian clocks could create a host of problems, including gut dysbiosis, metabolic dysfunction, arrhythmias, and sudden cardiac death. While more evidence and studies in humans are needed, the emerging risks of disrupting circadian rhythms highlights the importance of studying lesser-recognized contributors to cardiovascular disease. Evidence is starting to surface about the long-term consequences of a career in firefighting, but we still have a limited understanding of the impact that daily firefighting activities have on the body.

We all love things that are bad for us—be it chocolate or Netflix binging. For me, that includes firefighting. The fried station food, the sleepless nights, the gear coated in carcinogens—not one of it was good for me. If I were to take the literature at face value, I might sleep easy knowing I had left those things behind, but I have now traded sleepless nights at the station for sleepless nights on the wards, which, we are starting to understand, might be just as dangerous as the dirty bunker gear full of cancer. That being said, if a paper comes out tomorrow showing absolute proof of the relationship between disrupted circadian rhythms, arrhythmias, and disrupted metabolism, you will still find me running around the ER at 2:00 AM. Sometimes the bad is worth it, but that should not limit us from delving into ways to improve the risks.

**REFERENCES**